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CUTANEOUS TESTS AND IMMUNIZATION IN DIPHTHERIA AND SCARLET FEVER

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CUTANEOUS testing for susceptibility to diphtheria and scarlet fever has been a widespread practice for many years. The reliability of the former is generally accepted. To immunize against diphtheria three antigens are now in use. Immunization of certain groups of persons, especially nurses and physicians, against scarlet fever is practicable,[1] but the reactions encountered in giving Dick toxin have been such that it has never become officially recommended as public health procedure. The following report is a survey of twenty years of cutaneous testing and immunization of student nurses at the contagious department of Cleveland City Hospital.

Since 1925, all student nurses who entered contagious service have been given Schick and Dick tests routinely. Those who had positive reactions were immunized against the antigen to which they were susceptible. For about ten years all tests and injections for our own and for nurses from other hospitals affiliated with City Hospital were carried out at the City Hospital by one of us or by the residents under his direction.

Since any health procedure is valuable only if all physicians can use it, the tests and immunization were done in the subsequent ten years by the various residents and members of the visiting staffs of the corresponding schools. For a few years some of each new lot of nurses were checked by random sampling, but results, while not always the same, were not sufficiently divergent to be statistically different. The data of the second ten years then were culled from

From the Jack and Heinz Laboratories, the Department of Contagious Diseases, City Hospital, and the Department of Pediatrics, Western Reserve University.

1. (*a*) Rhoads, P. S: Skin Tests and Immunization Against Scarlet Fever and Diphtheria, J. A. M. A. **97**:153 (July 18) 1931. (*b*) Hektoen, L., and Johnson, C.: Prevention of Diphtheria and Scarlet Fever in Nurses, ibid. **102**:41 (Jan. 6) 1934. (*c*) Anderson, G. W., and Reinhardt, W. I.: Scarlet Fever Immunization of Nurses, J. Infect. Dis. **57**:136, 1935.

innumerable and changing sources. The data reported are contained in the accompanying record.

The student nurses have come from thirty-nine different hospitals, eleven of which are in Cleveland or its suburbs; the remainder of the hospitals are in smaller Ohio towns. The age range was approximately from 19 to 25 years.

Over five thousand Schick tests were done. The results are shown in table 1.

A striking feature of this table is the high rate of positive reactions to the Schick tests among this group of young adults. The distribution by five year periods is fairly constant. The figure of 49.7 per cent for positive reactions is in pronounced contrast to the figure of 14 per cent found among persons over 17 years old, by Schick, Park and Zingher.[2]

TABLE 1.—*Results of Schick Tests Before Immunization, 1925-1945*

Years	Positive		Negative		Pseudo		Total
	Number	Percentage	Number	Percentage	Number	Percentage	
1925-1929	161	58.6	113	41.0	1	0.4	275
1930-1934	110	40.7	160	59.3	0	0	270
1935-1939	695	50.9	667	48.9	3	0.2	1,365
1940-1944	1,224	50.4	1,201	49.4	5	0.2	2,430
1945	317	45.0	371	52.6	17	2.4	705
Total	2,507	49.7	2,512	49.8	26	0.5	5,045

A low rate of susceptibility in adults is thought to be brought about by repeated subclinical infections with Corynebacterium diphtheriae during childhood. An antitoxic immunity is gradually built up so that theoretically most adults, especially those living in areas of dense population and frequent epidemics, should give negative reactions to the Schick test. Schick, in Vienna, and Park and Zingher, in New York city, found this true from 1913 to 1921. This was not the case in Cleveland from 1925 to 1945. Other investigators have found similar high rates of positivity among young adults. Hektoen and Johnson in Chicago found that nearly 70 per cent of their student nurses had positive reactions. In a small but interesting study Wright and Clark [3] in London found that 57.5 per cent of 250 women had positive Schick reactions post partum and that over half of the infants of these women had positive reactions. These authors could not believe that there was actually so high a rate of susceptibility to diphtheria in these

2. Schick, B.: Diphtheria, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1945, vol. 2, chap. 4.

3. Wright, G. P., and Clark, W.: Schick Reactions in Recently Confined Women and Their Infants, Brit. M. J. 2:146, 1944.

women and felt, as had Glenny,[4] that there are persons with positive reactions to the Schick test who are immune or potentially immune.

An animal once immunized is capable of a secondary response to a stimulating dose of toxin. Glenny cites the fact that in many persons with positive reactions to the Schick test, particularly adults, the small amount of toxin used in doing the test often acts as the stimulating dose, so that the reaction to another Schick test two weeks later is negative. Completely nonimmune persons require much more toxin and a much longer time to give a negative reaction. The former persons were called by Glenny "Schick positive immune," or if by flocculation tests they had actually no circulating antibody in their serum but still gave a secondary response, they are potentially immune.

Forty-nine and eight-tenths per cent of the student nurses at City Hospital had negative reactions; the rest may not have come in

TABLE 2.—*Original Schick Reactions of Nurses in Cleveland Hospitals Compared with Reactions of Nurses from Hospitals of Smaller Communities, 1925 to 1945, Inclusive* *

	Reactions				
	Positive		Negative		
	Number	Percentage	Number	Percentage	Total
Nurses from Cleveland hospitals	1,585	50.9	1,528	49.1	3,113
Nurses from hospitals of smaller communities	922	48.4	984	51.6	1,906
Totals	2,507	49.9	2,512	50.1	5,019

* Pseudo reactions are excluded.

contact with organisms, especially since the incidence of diphtheria in Cleveland has been low since 1927,[5] giving them little opportunity of transient subclinical infection with C. diphtheriae. On the other hand, in Vienna and in New York city, at the time when Schick and Park and Zingher collected their data the incidence of diphtheria was high and presumably transient carriers of diphtheria were frequently getting stimulating doses of toxin; hence the percentage of persons having negative reactions to the Schick test was greater.

Table 2 was compiled to determine whether density of population had an effect on the results of Schick tests in these young adults. Two and five-tenths per cent more of the nurses from hospitals in smaller towns had negative Schick reactions than did nurses from Cleveland hospitals, though statistically this difference is not significant ($x/\sigma=1.7$). Why density of population made no difference in the apparent immunity

4. Glenny, A. T.: The Principles of Immunity Applied to Protective Inoculation Against Diphtheria, J. Hyg. **24**:301, 1925.

5. Doull, J. A., and Schuman, L. M.: Diphtheria Infection and Morbidity in Cleveland, 1937-1939, Am. J. Pub. Health (supp.) **30**:16, 1940.

rate is not clear. Many of the smaller towns, however, such as Canton and Akron, Ohio, and Buffalo, from which these students come, are really sizable cities although smaller than Cleveland. Grossman's studies in 1938-1939 [6] also indicated that rural areas in Virginia do not have less negative reactors to the Schick test than do urban areas.

Attacks of bacterial and toxic diseases may or may not impart a good and lasting immunity. The difference in rates of negativity to the test between those nurses who had had diphtheria and those who had not was only 5.8 per cent. There were more nurses with negative reactions among those who had had diphtheria, but the difference is not statistically significant ($x/\sigma = 1.5$).

TABLE 3.—*Original Schick Reactions of Nurses Who Had Had Diphtheria Compared with Reactions of Those Who Had Not, 1936 to 1945, Inclusive* *

	Reactions				
	Positive		Negative		
	Number	Percentage	Number	Percentage	Total
Had diphtheria	77	44.5	96	55.5	173
No diphtheria	2,039	50.3	2,011	49.7	4,050
Totals	2,116	50.1	2,107	49.9	4,223

* Pseudo reactions are excluded.

The rate of positive Schick reactions among persons who have had diphtheria is surprisingly high (44.5 per cent). Many of these nurses may have been potentially immune and needed only a stimulating dose of toxin to raise their antibody titer to the Schick level. Had they all been tested within a year after recovery from diphtheria there would probably have been a much higher rate of negative reactions to the Schick test.

IMMUNIZATION AGAINST DIPHTHERIA

In 1913, von Behring introduced the use of toxin-antitoxin. This agent has been used extensively, although it has certain disadvantages, chief of which is that it contains horse serum and therefore frequently sensitizes persons immunized. It has been pointed out that this is especially serious in student nurses [7] because they are heavily exposed to diphtheria and may contract the disease in spite of immunization. In such an event, if they are sensitive to horse serum, the most effective therapy, diphtheria antitoxin, may cause serum reactions. Toxin-antitoxin also takes a long time, often a year to effect immunity. Ramon, in 1924, eliminated horse serum from his antigen agent by detoxifying the toxin with solution of formaldehyde, the specific toxin

6. Grossman, W.: A Schick Test and Diphtheria Carrier Survey of White School Children in Virginia, Am. J. Pub. Health (supp.) **30**:8, 1940.

7. Toomey, J. A.: Active Immunity, J. A. M. A. **119**:18 (May 2) 1942.

losing its toxic effect but retaining its antigenic properties. More recently alum-precipitated toxoid has been developed and promises to be superior to the other two agents.

IMMUNITY RECORD

Name..... Age..... Sex..... Color.....

Address: Street..... City-Town..... State.....

SMALLPOX VACCINATION: Method:.....1st on....., Result.....;

2nd on....., Result.....; 3rd on....., Result.....; 4th on....., Result.....

SCHICK TEST—Before immunization was....., on .....

T(oxin) A(ntitoxin), T(oxoid), A(lum) P(recipitated) T(oxoid). Cross out types not used.

1st dose of.....on....., Reaction.....; 2nd dose of.....on....., Reaction.....;

3rd dose of.....on....., Reaction.....; 4th dose of.....on....., Reaction.....;

5th dose of.....on....., Reaction.....; 6th dose of.....on....., Reaction.....;

SCHICK TEST—after immunization was.....on.....

.....

.....

DICK TEST—Before immunization was.....on.....

DICK TOXIN—5 Doses. Number of units used—Fill in blanks.

1st dose of.....on....., Reaction.....; 2nd dose of.....on....., Reaction.....

3rd dose of.....on....., Reaction.....; 4th dose of.....on....., Reaction.....

5th dose of.....on....., Reaction.....;

DICK TEST—after immunization was.....on.....

.....

Tuberculin Test—How done—Intradermal, Patch, etc. .....

Dilution of material used..... Results: 1st.....; 2nd.....; 3rd.....; 4th.....

TYPHOID PARATYPHOID

1st injection on ....., Reaction: .....

2nd injection on ....., Reaction: .....

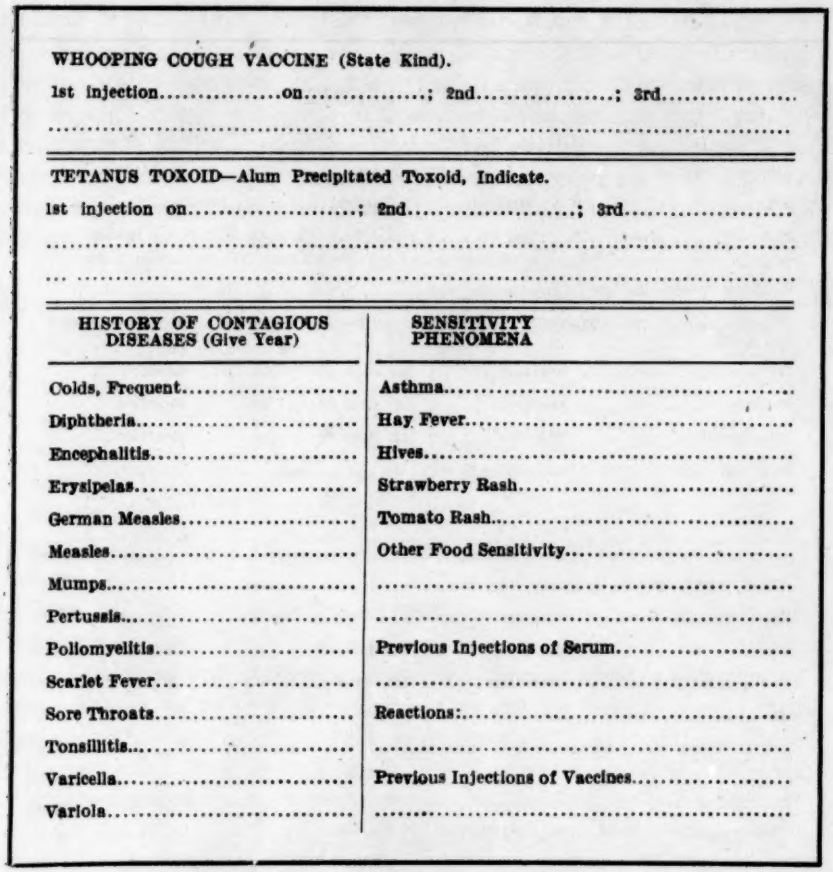
3rd injection on ....., Reaction: .....

Subsequent injections: .....

Fig. 1.—Form for immunity record (front of card).

Table 4 shows the results of diphtheria immunization of student nurses at Cleveland City Hospitals and affiliating hospitals over a twenty year period. Immunization against any disease is never perfect after one series of injections. Here an over-all failure rate of 14.6 per cent was found. Both toxoid and alum-precipitated toxoid had

a significantly lower rate of failures than did toxin-antitoxin. On the basis of effectiveness in reversing the Schick reaction from



WHOOPING COUGH VACCINE (State Kind).

1st injection.....on.....; 2nd.....; 3rd.....

.....

TETANUS TOXOID—Alum Precipitated Toxoid, Indicate.

1st injection on.....; 2nd.....; 3rd.....

.....

... .

HISTORY OF CONTAGIOUS DISEASES (Give Year)	SENSITIVITY PHENOMENA
Colds, Frequent.....	Asthma.....
Diphtheria.....	Hay Fever.....
Encephalitis.....	Hives.....
Erysipelas.....	Strawberry Rash.....
German Measles.....	Tomato Rash.....
Measles.....	Other Food Sensitivity.....
Mumps.....	.....
Pertussis.....	.....
Poliomyelitis.....	Previous Injections of Serum.....
Scarlet Fever.....	.....
Sore Throats.....	Reactions:.....
Tonsillitis.....	.....
Varicella.....	Previous Injections of Vaccines.....
Variola.....	.....

Fig. 2.—Form for immunity record (back of card).

TABLE 4.—*Diphtheria Immunization, 1925 to 1945*

	Toxin-Antitoxin	Toxoid	Alum-Precipitated Toxoid	Totals
Number immunized.....	726	441	745	1,912
Percentage of the total immunized by the Noted method.....	38.0	23.1	38.9	
Number reversing Schick reaction.....	597	384	651	1,632
Percentage reversing Schick reaction.....	82.3	87.1	87.4	85.4
Percentage of failures.....	17.7	12.9	12.6	14.6

positive to negative one could discard toxin-antitoxin as the antigen of choice. The difference found between the effectiveness of the two toxoids is negligible in this series.

Unfortunately, efficacy cannot be the only factor in determining the best immunizing agent. Unpleasant side reactions are encountered in using any of the materials. The least reactions were met with in using toxin-antitoxin; plain toxoid gave the most, and alum-precipitated toxoid was between, 5.6 per cent of those immunized having undesirable reactions. Nearly all the reactions were local in character—usually soreness and induration at the site of injection. Generalized reactions were rare with all three of the diphtheria antigens.

Alum-precipitated toxoid often is effective when given in a single dose. In children Volk and Bunney found that a single injection of alum-precipitated toxoid immunized much more often than two doses of plain toxoid at three week intervals.[8] Toxin-antitoxin requires at least three injections at monthly intervals to give satisfactory results. Alum-precipitated toxoid given in two doses of 1 cc. each

TABLE 5.—*Untoward Reactions Encountered in Diphtheria Immunization, 1936 to 1945*

	Toxin-Antitoxin	Toxoid	Alum-Precipitated Toxoid	Totals
Number immunized	617	407	738	1,762
Number of reactions	16	44	41	101
Percentage of reactions	2.6	10.8	5.6	5.7

at an interval of one month is the most effective and convenient method of immunizing against diphtheria. But because reactions were encountered with this agent in adults the United States Public Health Association Subcommittee on Diphtheria recommended that plain toxoid or toxin-antitoxin be used to immunize certain groups of adults.[9] In our series alum-precipitated toxoid was superior in all respects to plain toxoid. It was more efficient and convenient than toxin-antitoxin though it caused more reactions, and does not sensitize. But the reactions were nearly always mild. We always first tested with 0.1 cc. subcutaneously and noted the effect. If no untoward reactions were noted, we gave 0.4 cc. the next week and 1 cc. the next month. Alum-precipitated toxoid has become the agent of choice for immunizing student nurses with positive reactions to the Schick test against diphtheria at Cleveland City Hospital. All adults should be given a Schick test, and only the ones with positive reaction should receive injections.

8. Volk, V. K., and Bunney, W. E.: Diphtheria Immunization with Fluid Toxoid and Alum Precipitated Toxoid, Am. J. Pub. Health (supp.) **30**:42, 1940.

9. Recommendations of Subcommittee on Diphtheria of U. S. Public Health Association, Am. J. Pub. Health (supp.) **30**:47, 1940.

That immunization of student nurses against diphtheria is valuable is shown by the fact that only 4 cases of diphtheria have occurred among the nurses in twenty years, an incidence of 0.06 per cent. Though it must be admitted that the chances for exposure are much less than years ago, Hektoen and Johnson [1b] found that the incidence of diphtheria dropped from 18.4 to 0.89 per cent after immunization had been carried out among their nurses.

THE DICK TEST

Immunity to scarlet fever is an immunity coming on after an attack of the disease or as a result of repeated subclinical infections with toxin-producing hemolytic streptococci.[10] It is not our purpose at this time to consider whether or not we merely are protecting against erythrogenic toxin.

TABLE 6.—*Results of Dick Tests Before Immunization, 1925-1945*

	Reactions				
	Positive		Negative		
Years	Number	Percentage	Number	Percentage	Totals
1925-1929	443	41.9	613	58.1	1,056
1930-1934	319	36.6	553	63.4	872
1935-1939	574	39.3	890	60.7	1,464
1940-1944	933	36.8	1,604	63.2	2,537
1945	326	44.5	406	55.5	732
Totals	2,595	38.9	4,066	61.1	6,661

Over 6,500 student nurses were given the Dick test between 1925 and 1945; the results are shown in table 6. Of the total 61.1 per cent had negative reactions. The rates are seen to be rather constant for five year periods. In similar surveys of student nurses Rhoads, in Chicago, and Anderson and Reinhardt, in Boston, found 58.4 per cent and 47.7 per cent negative Dick reactions respectively. Hektoen and Johnson,[1b] also in Chicago, found 50.4 per cent of their student nurses had negative reactions. While the agreement of these studies is not close, it is much better than those for susceptibility to diphtheria. It would seem that the distribution of subclinical infections in scarlet fever is much more prevalent than in diphtheria.

The past history with respect to scarlet fever was available only for nurses tested since 1936. In table 7 the results of the Dick test are separated into two groups—for nurses who had had scarlet fever previous to testing and for those who had not. It is seen that only 8.4 per cent more of those who had had scarlet fever had negative Dick reactions.

10. Dick, G. F., and Dick, G. H.: A Skin Test for Susceptibility to Scarlet Fever, J. A. M. A. **82**:265 (Jan. 26) 1924.

The difference is relatively small, but unlike the same calculation in diphtheria it is significant ($x/\sigma = 9.8$).

There is a demonstrable tendency for an attack of scarlet fever to impart an immunity which lasts for a considerable period of time. Perhaps the original antibody titer is bolstered from time to time by subclinical infections with toxin-producing streptococci. In Cleveland it

TABLE 7.—*Original Reactions to Dick Tests of Nurses Who Had Had Scarlet Fever Compared to Reactions of Nurses Who Had Not; 1936 to 1945, Inclusive*

	Reactions				
	Positive		Negative		
	Number	Percentage	Number	Percentage	Total
Had scarlet fever	196	23.8	628	76.2	824
Did not have scarlet fever	529	41.2	2,097	57.8	3,626
Totals	725	38.8	2,725	61.2	4,450

seems that such infections occur much more frequently than do infections with C diphtheriae.

Table 8 shows that nurses from hospitals of smaller communities have a higher rate of negative reactions to the Dick test than do nurses from Cleveland hospitals. The reason for this is not clear.

TABLE 8.—*Original Dick Reactions of Nurses in Cleveland Hospitals Compared to Reactions of Nurses from Hospitals of Smaller Communities, 1925 to 1945, Inclusive*

	Reactions				
	Positive		Negative		
	Number	Percentage	Number	Percentage	Total
Nurses from Cleveland hospitals	1,588	40.8	2,295	59.2	3,883
Nurses from hospitals of smaller communities	1,077	36.2	1,771	36.8	2,778
Totals	2,595	38.9	4,066	61.1	6,661

The Dick test is a good but not a perfect indicator of immunity to scarlet fever. In this series 74, or 1.8 per cent, of those with originally negative reactions to the Dick test who were nurses contracted scarlet fever while under heavy exposure. The test is an essential part of the program of immunization, because reactions to immunizing doses of Dick toxin as practiced are too frequent and too severe to warrant blanket immunization of all nurses.

IMMUNIZATION AGAINST SCARLET FEVER

Since 1925, student nurses who react positively to the Dick test have routinely been immunized with Dick toxin and have subsequently

been retested. For a time a three dose immunizing course was tried, but it was later abandoned in favor of a five dose course. Five injections of toxin at weekly intervals were given. The first dose contains 500 cutaneous test doses of toxin, the second 2,000, the third 8,000, the fourth 25,000 and the last 100,000. In some cases in which reactions were encountered early in the course the doses were split and given over an extended period of time.

TABLE 9.—*Effectiveness of Immunization Against Scarlet Fever; Dick Reactions After Immunization, 1925 to 1945* *

	Reactions		
	Positive	Negative	Totals
Number	236	1,926	2,162
Percentage	10.9	89.1	

* Only those are included who originally had positive reactions to the Dick test.

Two thousand, one hundred and sixty-two nurses were immunized and then retested. The reactions of 89.1 per cent had become negative. Of those who had reversed their Dick reaction only 15, or 0.8 per cent, contracted scarlet fever. Other investigators [1bc] reported that before 1924, 7 to 8 per cent of the new nurses in two contagious hospitals would contract scarlet fever. During the twenty years covered in this report 95, or 1.4 per cent, of those who originally had negative reactions to the Dick test or who were immunized contracted scarlet fever.

TABLE 10.—*Frequency of Reactions in Immunization Against Scarlet Fever, 1936 to 1946*

Number Immunized	Number of Reactions	Percentage with Reactions
1,575	453	28.7

This includes 6 nurses who were immunized but whose reaction to the Dick test remained positive. The reduction from about 8 per cent to 1.4 per cent in the incidence of scarlet fever has proved to be of economic advantage to both hospital and nurses.

The chief objection to immunization with Dick toxin is the high incidence of unpleasant reactions.

In this series 28.7 per cent of those immunized had reactions. The severity of reactions ranged from mild local soreness to scarlet fever in miniature resulting in short hospitalization. Table 11 demonstrates the frequency with which the various reactions occurred. Often multiple reactions were suffered by 1 nurse.

Nausea and vomiting were the commonest of the systemic reactions. This is not surprising since, as Henry [11] pointed out, scarlet fever streptococcus toxin is a specific emetic. Scarlatiniform rashes were relatively uncommon. However, 5.8 per cent of all the nurses immunized had pains in the joints. Healey [12] found that about 3 per cent of immunized nurses had pains in the joints. If the toxin was destroyed by boiling the resulting proteins usually did not produce these pains. He concluded that the specific toxin was the cause of the symptoms.

TABLE 11.—*Frequency of Various Types of Reactions Encountered in Immunization Against Scarlet Fever, 1936 to 1946*

Type of Reaction	Number
Local	188
Nausea and vomiting	116
Pains in joints	92
Fever	91
Headache	68
Rash	30
Not specified	130

Later Rhoads and Afremow [13] found an unusually high incidence of previous or subsequent manifestations of rheumatic fever among those persons having pains in the joints during immunization. There was, however, nothing to indicate that rheumatic fever was reactivated by the immunization itself.

Table 12 indicates that most of the subjects reacted after the first dose of toxin if they were going to react at all. In other words, 500 cutaneous test doses of toxin were enough to provoke a reaction in those

TABLE 12.—*Frequency of Reactions After Each Dose of Scarlet Fever Toxin*

Dose	Number of Reactions
1	249
2	56
3	83
4	34
5	31

who were vulnerable, while 100,000 cutaneous test doses usually caused no reaction in the nonvulnerable.

Between 20 and 30 per cent of persons immunized can be expected to show unpleasant reactions, the majority of which will be local. A

11. Henry, J. N.: A Study of Active Immunization Against Scarlet Fever, J. A. M. A. **105**:488 (Aug. 17) 1935.

12. Healey, C. E.: The Cause of Joint Pains Occurring During Active Immunization with Scarlet Fever Streptococcus Toxin, J. A. M. A. **108**:628 (Feb. 20) 1937.

13. Rhoads, P. S., and Afremow, M. L.: Joint Pains Caused by Sterile Streptococcus Toxin, Ann. Int. Med. **19**:60, 1943.

small number will have reactions so severe that they will have to be hospitalized or kept in bed for from one to five days. Nausea and vomiting and pains in the joints will be the most frequent of the systemic reactions. Over a period of years a small fraction of persons with a negative reaction to the Dick test or who have become immunized will contract scarlet fever when heavily exposed.

SUMMARY

At Cleveland City Hospital nearly 50 per cent of a group of student nurses were found to give positive reactions to the Schick test. Neither the density of population of the area they came from nor the fact that some had had diphtheria significantly altered the rate of positivity.

Alum-precipitated toxoid in our hands was found to be the best immunizing agent against diphtheria in these young adults.

In over 6,500 Dick tests on student nurses, 38.9 per cent of the reactions were positive. Persons from smaller towns had a higher percentage of negative reactions than did persons from Cleveland hospitals. Persons who had had scarlet fever had a higher rate of negative reactions than those who had not had scarlet fever. The Dick test is a good but not perfect indicator of immunity to scarlet fever.

Immunization with Dick toxin was 89.1 per cent effective in that the cutaneous test was reversed.

Twenty-eight and seven-tenths per cent of those immunized had reactions. Some reactions were serious, but most were local.

SERUM LEVELS OF VITAMIN A IN CHILDREN

A Comparison Following the Oral and Intramuscular Administration of Vitamin A in Oily and in Aqueous Mediums

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BLACKFAN and Wolbach [1] have reported that "histologic evidences of A avitaminosis may occur in infants who are receiving an amount of vitamin A in their diet usually accepted as meeting the minimal protective needs of the body." Similar histologic changes have been observed by one of us (B. K.) in children with chronic diarrhea and cystic fibrosis of the pancreas who received amounts of vitamin A much larger than the considered adequate dose.

It has been shown by May and his colleagues [2] and Chesney and McCoord [3] that impaired intestinal absorption of vitamin A exists in children with celiac disease, cystic fibrosis of the pancreas, obliteration of the bile ducts and cretinism.

In an effort to circumvent this barrier to the absorption of vitamin A, the latter was administered by intramuscular injection.[4] Although McCoord and Breeze [5] obtained an elevation of the vitamin A level in the serum of dogs following intramuscular injection of the vitamin A in oil, we obtained no such result with children. A relatively flat tolerance curve was obtained in each of the 4 patients studied who had

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From the Pediatric Research Laboratory and the Pediatric Department of The Jewish Hospital.

1. Blackfan, K. D., and Wolbach, S. B.: Vitamin A Deficiency in Infants, J. Pediat. **3**:679, 1933.

2. May, C. D.; Blackfan, K. D.; McCreary, J. F., and Allen, F. H.: Clinical Studies of Vitamin A in Infants and in Children, Am. J. Dis. Child. **59**:1167 (June) 1940.

3. Chesney, J., and McCoord, A.: Vitamin A of Serum Following Administration of Haliver Oil in Normal Children and in Chronic Steatorrhea, Proc. Soc. Exper. Biol. & Med. **31**:887, 1934.

4. Natural distilled esters of vitamin A in sesame oil; 1 cc. is the equivalent of 50,000 U. S. P. units.

5. McCoord and Breeze, cited by Clausen, S. W.: The Absorption of Vitamin A and Storage in the Tissues, in Harvey Lectures, 1942-1943, Lancaster, Pa., Science Press Printing Company, 1943, vol. 38, pp. 199 and 216.

50,000 U. S. P. units injected into the buttocks. The results are listed as the first 4 cases in table 1. These observations have been confirmed by a recent publication of Cienfuegos.[6]

Lemley and his colleagues [6a] have shown that liver stores of rats given intramuscular injections are 1.7 per cent of those fed an equal amount of vitamin A orally.

TABLE 1.—*Vitamin A Levels in the Serum After the Intramuscular Injection of an Oily and an Aqueous Preparation of Vitamin A*

Name	Age, Years	Diagnosis	Oily Preparation of Vitamin A Esters in Sesame Oil	Vitamin A Levels, Micrograms/100 Cc.				
				Fasting	3*	6*	9*	12*
J. R.	13	Acute primary atypical pneumonia; asthma; vitamin A deficiency	50,000 U.S.P. units	22.4	12.6	12.6	11.2	....
M. M.	1½	Pneumonia, lower lobe of right lung; congenital heart disease	50,000 U.S.P. units	14.0	14.8	16.8	14.3	14.5
N. C.	3	Glomerulonephritis, nephrotic stage	50,000 U.S.P. units	60.2	74.2	58.8	60.2	61.6
C. A.	2	Cystic fibrosis of the pancreas; bronchopneumonia	50,000 U.S.P. units	64.4	67.2	67.2	72.8	....
			Mean.....	40.3	42.2	39.0	39.6	....
			Aqueous Preparation of Vitamin A Acetate					
H. P.	9	Ulcerative colitis; chronic necrotizing infection of right foot	4,000 U.S.P. units per pound of body weight	25.2	22.7	28.3	43.4	40.9
M. C.	10	Purulent cervical adenitis; incision and drainage of abscess	4,000 U.S.P. units per pound of body weight	20.5	27.7	35.3	61.3	63.9
D. F.	5½	Bronchopneumonia, right; pleural effusion, right; nasopharyngitis; catarrhal otitis media, acute, right	4,000 U.S.P. units per pound of body weight	36.4	51.5	65.3	238.0	
G. M.	7½	Acute nasopharyngitis; infectious mononucleosis; healed pulmonary tuberculosis, childhood type	4,000 U.S.P. units per pound of body weight	82.9	93.8	91.9	118.0	
			Mean.....	41.3	48.9	55.2	115.0	

* Hours after test dose of vitamin A.

In the hope of increasing the absorption of vitamin A following intramuscular administration, an aqueous dispersion of vitamin A [7] was injected into the buttocks to the extent of 4,000 U. S. P. units per pound

6. Cienfuegos, S.: Comparison of Absorption of Vitamin A After Oral and Muscular Administration in Normal Children, J. Pediat. **28**:191, 1946.

6a. Lemley, J. M.; Brown, R. A.; Bird, O. D., and Emmett, A. D.: Absorption and Storage of Vitamin A in the Liver of the Rat, J. Nutrition **33**:53 (Jan.) 1947.

7. This product contained 33,000 U. S. P. units of vitamin A acetate in 1 cc. with 1 per cent procaine hydrochloride and phenylmercuric acetate, 1 to 10,000, and 7.5 volumes per cent of sorbitan monolaurate polyoxyalkylene derivative as dispersing agent.

(8,818 units per kilogram) of body weight. As revealed in the last 4 cases in table 1, there was a distinct rise nine hours after the injection. The rise varied between 18.2 and 202 micrograms per hundred cubic centimeters. A twelve hour specimen of blood was also taken in 2 of the cases to determine whether the rise continued after nine hours. This was found not to be the case.

This method was discontinued for two reasons: First, a local reaction occurred at the site of the injection which may have been due to the relatively large volumes of preparation injected. For a 10 pound (4,536 Gm.) child, this would amount to 1.2 cc. Second, a more efficient means of raising the vitamin A level by oral administration was found.

The preparation [8] used was an aqueous dispersion of fish liver oil supplemented by other vitamins, and is designated in this paper as aqueous dispersion I. The dispersing agent used was the ethylene oxide derivative of sorbitan monolaurate, which is closely related in dispersing properties to the mannitan derivative described by Carr and Krantz,[9] who reported that mannitan monolaurate combined with twenty moles of ethylene oxide was not found to be toxic when fed to white rats and monkeys over a period of two years. Krantz [10] stated that "our studies show no difference in the toxicity of the two compounds in two species of animals and from a toxicological standpoint they may be used interchangeably."

Vitamin A tolerance tests were performed on several children showing impaired intestinal absorption as revealed by low vitamin A absorption curves following the feeding of 6,000 U. S. P. units of vitamin A per pound (13,228 per kilogram) of body weight in the form of fish liver oil (percomorph liver oil) and by a high fat content in the stool. Both the fish liver oil and aqueous dispersion I were given in orange juice. This mixture was prepared immediately before use, in order to eliminate any effect dilution with orange juice might have on the stability of the vitamin A. The results are represented by the first 5 cases in table 2.

It is clearly evident that with aqueous dispersion I an earlier and more pronounced rise is obtained than with the fish liver oil. In fact,

8. The preparation is called "Vifort." Each 0.6 cc. contained: 6,000 U. S. P. units of vitamin A, 1,200 U. S. P. units of vitamin D, 1.8 mg. of thiamine hydrochloride, 0.6 mg. of riboflavin, 0.3 mg. of pyridoxine hydrochloride, 60 mg. of ascorbic acid, 3 mg. of nicotinamide, 1.2 mg. of calcium pantothenate and 132 mg. of extract of rice polishings, and also contained choline, inositol and biotin vitamers, and 11 volumes per cent of sorbitan monolaurate polyoxyalkylene derivative, which is the dispersing agent.

9. Carr, C. J., and Krantz, J. C., Jr.: Metabolism of Sugar Alcohols and Their Derivatives, in Pigman, W. W., and Wolfrom, M. L.: Advances in Carbohydrate Chemistry, New York, Academic Press, 1945, vol. 1, pp. 175 and 187.

10. Krantz, J. C., Jr.: Personal communication to the authors.

the curve compares favorably with that obtained in a normal child when fish liver oil is used, the average maximum elevation being 142 micrograms per hundred cubic centimeters as compared with an average maximum elevation of 34.1 micrograms when fish liver oil was used. If the elevations at the end of three hours are compared, an average rise of 12.6 micrograms per hundred cubic centimeters was obtained with the fish liver oil as compared with an average rise of 134.5 micrograms with aqueous dispersion I.

TABLE 2.—*A Comparison of the Vitamin A Tolerances in Children Using Fish Liver Oil and Aqueous Dispersion I*

Name	Age	Diagnosis	Preparation	Vitamin A Levels, Micrograms/100 Cc. Fasting	3*	6*	9*
A. C.	7½ mo.	Celiac syndrome on an allergic basis	Fish liver oil	27.2	42.3	46.8	47.6
			Aqueous dispersion I	58.8	266.0	136.0	21.3
			Fish liver oil	52.9	92.2	68.3	68.3
B. G.	8 mo.	Celiac syndrome; bilateral otitis media	Fish liver oil	45.4	44.5	62.7	65.8
			Aqueous dispersion I	75.4	282.0	122.0	108.0
			Fish liver oil	65.2	60.8	53.3	50.0
S. L.	11 yr.	Celiac syndrome; pneumonia, upper lobe, left lung, due to Klebsiella pneumoniae	Fish liver oil	40.1	56.6	65.5	109.0
			Aqueous dispersion I	25.8	95.5	70.3	68.9
			Fish liver oil	25.3	49.3	59.1	61.3
B. K.	1½ mo.	Celiac syndrome; pneumonia	Fish liver oil	28.6	33.6	101.0	110.0
			Aqueous dispersion I	26.0	93.3	138.0	97.5
J. K.	5 mo.	Celiac syndrome; bronchopneumonia	Fish liver oil	19.6	25.8	24.9	22.4
			Aqueous dispersion I	21.6	137.0	79.0	50.7
		Mean.....	Fish liver oil	38.0	50.6	60.2	66.8
			Aqueous dispersion I	40.5	175.0	109.0	69.3
A. Z.	12 yr.	Undescended testicle, left orchidopexy	Fish liver oil	43.1	239.0	154.0	95.1
			Aqueous dispersion I	43.1	427.0	214.0	108.0
D. A.	12 yr.	Undescended testicle; left orchidopexy	Fish liver oil	23.8	91.9	142.0	188.0
			Aqueous dispersion I	31.7	331.0	500.0	191.0
M. J.	10 yr.	Acute rheumatic fever with polyarthritis and carditis	Fish liver oil	44.0	75.6	113.0	86.3
			Aqueous dispersion I	40.9	257.0	210.0	170.0
H. R.	11 yr.	Bronchiectasis	Fish liver oil	58.5	60.5	103.0	210.0
			Aqueous dispersion I	56.6	81.8	376.0	158.0
H. F.	3½ mo.	Parenteral diarrhea; nasopharyngitis; otitis media, catarrhal, acute	Fish liver oil	43.7	96.6	86.2	70.0
			Aqueous dispersion I	70.3	223.0	167.0	139.0
		Mean.....	Fish liver oil	42.6	113.0	120.0	130.0
			Aqueous dispersion I	48.5	250.0	293.0	153.0

* Hours after test dose of 6,000 U.S.P. units per pound of body weight.

To verify these observations fully, a tolerance test for fish liver oil was performed in some patients after, as well as before, the tolerance test for aqueous dispersion I. All the patients evidencing impaired intestinal absorption had been on vitamin A medication (10 to 20 drops of percomorph liver oil per day) prior to the performance of the tolerance tests. Therefore, the fasting vitamin A levels are probably higher than on admission. This effect of continued administration of vitamin A on the fasting blood level was pointed out by May and his colleagues.[2]

In view of these results, the absorption curves for aqueous dispersion I were compared with the curves for fish liver oil in children showing no evidence of impaired intestinal absorption. The latter are represented by the last 4 cases in table 2. Again, the rise due to aqueous dispersion I is much greater and occurs earlier than that due to the fish liver oil. The average maximum elevation with aqueous dispersion I was 308 micrograms per hundred cubic centimeters; with fish liver oil it was only 133 micrograms.

To find an explanation for the higher blood levels when aqueous dispersion I was used, another preparation, similar to aqueous dispersion I but containing only the same fish liver oil and the same dispersing agent, was made. In this preparation, the concentration of the dispers-

TABLE 3.—*A Comparison of the Vitamin A Tolerances in Children Using Fish Liver Oil, Aqueous Dispersion I and Aqueous Dispersion II*

Name	Age	Diagnosis	Preparation	Vitamin A Levels. Micrograms/100 Cc. Fasting	3*	6*	9*
	12 yr.	Undescended testicle, left orchidopexy	Fish liver oil	43.1	239.0	154.0	95.1
			Aqueous dispersion I	43.1	427.0	214.0	108.0
			Aqueous dispersion II	43.1	1,322.0	310.0	152.0
D. A.	12 yr.	Undescended testicle, left orchidopexy	Fish liver oil	23.8	91.9	142.0	188.0
			Aqueous dispersion I	31.7	331.9	500.0	191.0
			Aqueous dispersion II	26.3	1,000.0	377.0	210.0
B. K.	1½ mo.	Celiac syndrome; pneumonia, upper lobe, left lung, due to Klebsiella pneumoniae	Fish liver oil	28.6	33.6	101.0	110.0
			Aqueous dispersion I	26.0	93.3	138.0	97.5
			Aqueous dispersion II	31.4	205.0	203.0	84.3
J. K.	5 mo.	Celiac syndrome; bronchopneumonia	Fish liver oil	19.6	25.8	24.9	22.4
			Aqueous dispersion I	21.6	137.0	79.0	50.7
			Aqueous dispersion II	23.5	142.0	145.0	62.7
		Mean.....	Fish liver oil	28.8	97.6	111.0	104.0
			Aqueous dispersion I	30.6	247.0	233.0	112.0
			Aqueous dispersion II	31.1	667.0	259.0	127.0

* Hours after test dose of 6,000 U.S.P. units per pound of body weight.

ing agent was increased to 20 volumes per cent. This was necessary in order completely to stabilize the solution. In aqueous dispersion I, a lesser concentration of the dispersing agent was needed, since the other components present also aided in the solubilization of the vitamin A. The concentration of vitamins A and D in both preparations was also the same. All other vitamins were absent. This preparation will be referred to as aqueous dispersion II. When tolerance tests for vitamin A were performed with aqueous dispersion II, the latter also being administered in dosages of 6,000 U.S.P. units per pound of body weight, a far greater rise was obtained than in the case of aqueous dispersion I. The results are listed in table 3.

In chart 1 is presented graphically a comparison of the vitamin A levels in a child with the celiac syndrome after the ingestion of fish

liver oil, aqueous dispersion I and aqueous dispersion II. In chart 2 is presented a comparison of the vitamin A levels in a normal child.

The average maximum rise with fish liver oil was 109 micrograms per hundred cubic centimeters, with aqueous dispersion I it was 270 micrograms, and with aqueous dispersion II it was 637 micrograms. Thus, it is evident that the rise obtained with aqueous dispersion II is far greater than that obtained with aqueous dispersion I and that the rise obtained with both of these preparations is greater than that obtained with fish liver oil. Therefore, from these results it appears that the increased absorption obtained with aqueous dispersions I and II is due to the dispersion per se of the fish liver oil in the aqueous mediums.

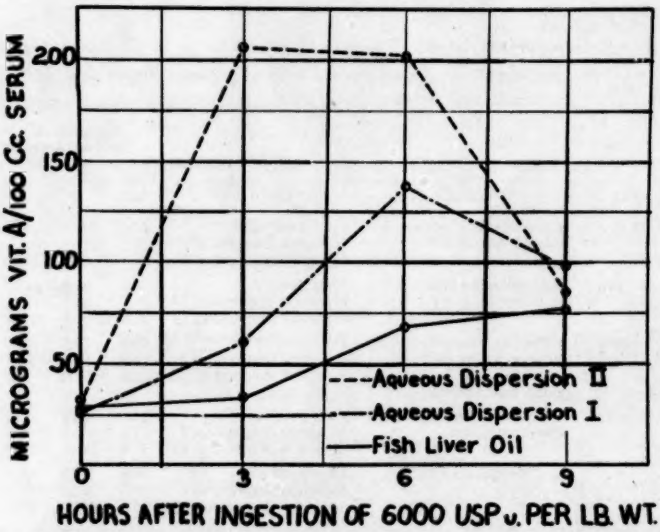

Chart 1.—A comparison of the vitamin A tolerances in a child with the celiac syndrome, using fish liver oil, aqueous dispersion I and aqueous dispersion II.

To account for the greater rise obtained with aqueous dispersion II as compared to aqueous dispersion I, it is possible that the vitamins other than those contained in fish liver oil partially inhibit the improved absorption due to aqueous dispersion, by retarding in some manner the absorption of vitamin A. A second possibility is that the higher concentration of the dispersing agent in aqueous dispersion II might be responsible for the greater absorption. In both postulates, the difference in absorption might be due to the effect on the particle size of the oil containing the vitamin A. For the absorption of paraffin, particle size has been shown to be an important factor by Frazer and his colleagues.[11]

11. Frazer, A. C.; Schulman, J. H., and Stewart, H. C.: Emulsification of Fat in the Intestines of the Rat and Its Relationship to Absorption, J. Physiol. **103**: 306, 1944.

The latter found that the finer the dispersion of the paraffin, the more rapid the absorption, providing that the average particle size was about 0.5 micron. In fact, it was as well absorbed as olive oil emulsion similarly treated and having the same degree of dispersion and stability. Unemulsified paraffin, on the other hand, was not absorbed at all. This point is being investigated further.

The data here presented bring up the interesting point whether efficient absorption of vitamin A depends in part on the ability of intestinal action to emulsify the vitamin A. This may be the explanation for the improved absorption of vitamin A reported by Adlersberg [12] in cases of sprue when lecithin was added to the vitamin A. Lecithin

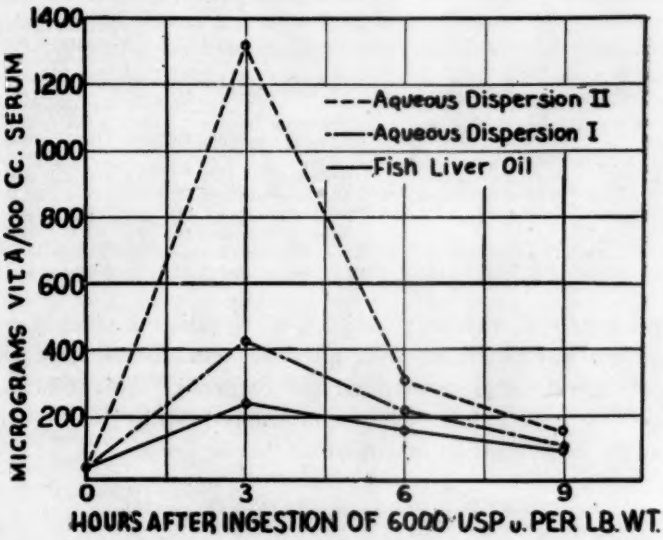

Chart 2.—A comparison of the vitamin A tolerances in a normal child, using fish liver oil, aqueous dispersion I and aqueous dispersion II.

is a well known emulsifier of fats, and its effect in increasing the absorption of vitamin A may be due to its emulsifying action rather than to any other specific property. In order to shed further light on this question, we hope to study the effect of other dispersing agents on the absorption of vitamin A.

In order to determine whether the dispersing agent present in aqueous dispersions I and II was responsible for raising the level of vitamin A in the serum by mobilizing vitamin A from the body tissues or by any other means, levels of vitamin A in the serum were determined after administration of an aqueous solution of the dispersing agent alone. In

12. Adlersberg, D.: Fat and Vitamin A Absorption in Sprue, New York State J. Med. **44**:606, 1944.

this preparation the dispersing agent, sorbitan monolaurate polyoxyalkylene derivative, was present in the same concentration as in aqueous dispersion I. The solution was administered on the same basis of body weight as the other preparations.

As a basis of comparison, tolerance tests for vitamin A were performed on the same children as had been given aqueous dispersion II. The results are listed in table 4. When the solution of the dispersing

TABLE 4.—*A Comparison of the Vitamin A Levels in the Serum in Normal Children After the Administration of Sorbitan Monolaurate Polyoxyalkylene Derivative and Aqueous Dispersion II*

Name	Age	Diagnosis	Preparation	Vitamin A Levels. Micrograms/100 Cc. Fasting	3*	6*	9*
J. R.	11 yr.	Pelvic abscess subsequent to ruptured appendix	Dispersing agent	38.1	36.4	39.1	39.1
			Aqueous dispersion II	19.6	840.0	532.0	314.0
S. R.	10 mo.	Fracture of middle third of left femur	Dispersing agent	20.0	19.3	20.5	20.2
			Aqueous dispersion II	30.8	613.0	101.0	70.0
		Mean.....	Dispersing agent	29.1	29.9	29.8	29.2
			Aqueous dispersion II	29.9	727.0	317.0	192.0

* Hours after test dose of 0.6 cc. of preparation per pound of body weight.

agent was employed without vitamin A, no elevation of vitamin A levels in the serum was obtained. But after the administration of aqueous dispersion II, the usual pronounced rise occurred. This indicates that the dispersing agent, alone, when administered orally had no apparent effect on the concentration of vitamin A in the serum.

CLINICAL DATA OF PATIENTS WITH CELIAC SYNDROME

CASE 1.—A. C., a 6 month old white boy, had a three week history of coughing and wheezing. The child had had a similar episode associated with wheezing and diarrhea at the age of 3 months which was corrected when his formula was changed from evaporated milk to "nutramigen." His stools were large, semisolid and green, but had no foul odor.

On admission he had a grunting type of respiration with a mild respiratory wheeze. The chest was clear, however. The abdomen was somewhat distended.

The child was found to have normal trypsin and amylase concentrations in the duodenal fluid. The glucose tolerance curve showed an increase of blood sugar, which was sustained after two hours, and a flat vitamin A absorption curve with an oily preparation of vitamin A. A gastrointestinal series showed segmentation and irregular peristaltic activity in the small bowel. The stool fat was 32.4 per cent of dry weight. Nasal smears revealed pronounced eosinophilia.

He was discharged on the twenty-ninth hospital day to the care of his private physician. When discharged he was getting only "nutramigen," banana and supportive vitamins and was still coughing and wheezing somewhat.

CASE 2.—B. G., an 8 month old white boy was admitted to the hospital with a four week history of diarrheal stools. This child had had diarrhea in early infancy

which was controlled with protein milk. He was subsequently changed to "similac." When he was 3 months old his parents noted the development of a "pot belly," and subsequently various formulas were tried. About one month prior to admission he began to have loose stools which did not respond to a protein milk diet. There had been no respiratory infections.

On admission the abdomen was distended and the buttocks atrophied, and he showed evidence of recent loss of weight. There was a bilateral otitis media.

The child was treated with sulfadiazine and put on a regimen combining starvation and parenteral administration of fluid. Within twenty-four hours feedings of protein milk were gradually started. The diarrhea was well controlled, and he was subsequently given a more liberal diet including cottage cheese, banana, chicken and vegetables. The otitis media cleared readily.

Laboratory Data.—Normal trypsin and amylase concentrations were obtained on duodenal drainage. A gastrointestinal series revealed irregular dilatation, segmentation and general loss of normal pattern of the small bowel; stool fat was 26.4 per cent of dry weight; the vitamin A tolerance curve was flat when an oily preparation of vitamin A was used, and a relatively flat glucose tolerance curve was obtained.

CASE 3.—S. L., an 11 year old white boy, was admitted to the pediatric service with a history of cough and fever of three weeks' duration. The child has been known to have the celiac syndrome since the age of 17 months and has been on a celiac dietary regimen since then.

On admission signs of consolidation were found in the lower lobe of the left lung, and these were confirmed by roentgenologic studies. The patient was treated with penicillin and made a complete recovery from his pneumonia.

After his recovery he was put on a regular diet. After this change he was found to have normal pancreatic enzymes on duodenal drainage; a gastrointestinal series revealed segmentation of the small bowel with areas of dilatation and constriction; cholecystograms (oral technic) were normal; there was a flat glucose tolerance curve and a rising vitamin A tolerance curve with percomorph liver oil.

The patient was discharged on the twenty-ninth hospital day with a gain in weight of 6 pounds (2.7 Kg.).

CASE 4.—B. K., a 10 week old white boy, was admitted to the hospital with a dry hacking cough and fever of two weeks' duration that had failed to respond to sulfadiazine therapy. He was found, on physical and roentgenologic examination, to have a pneumonic process in the left lung. This did not clear with penicillin therapy, and a bronchoscopic examination was made. Pus was obtained from the left main bronchus and Klebsiella pneumoniae was cultured. The child was given streptomycin, and the lung cleared, although the patient still coughed occasionally.

Since the patient's appetite was poor, his weight was constant and he was having large, foul stools, he was studied for evidence of celiac syndrome. Stool fat was 37.9 per cent of dry weight; normal trypsin and amylase concentrations were obtained on duodenal drainage; a gastrointestinal series revealed segmentation and dilatation of the loops of small bowel, and there was a somewhat flat vitamin A curve with percomorph liver oil and a normal glucose tolerance curve. He was placed on a diet of protein milk, bananas and cottage cheese and high in vitamins.

The patient was discharged on the eighty-second hospital day to the care of a private physician.

CASE 5.—J. K., a 2½ month old white boy, was admitted with the chief complaint of cough and intermittent cyanosis of two months' duration. The delivery and the neonatal history were normal; his weight at birth was 7 pounds, 2 ounces

(3,232 Gm.). A few days after leaving the nursery for newborn infants, an infection of the upper respiratory tract developed, with nasal discharge, followed by coughing, choking spells and cyanosis. A preadmission diagnosis of pulmonary atelectasis was made on the basis of physical and roentgenologic observations. There was no history of feeding difficulty or gastrointestinal disturbance.

Physical examination on admission revealed fair nutrition and good hydration; the infant's weight was 9 pounds, 8 ounces (4,309 Gm.). Scattered rhonchi were heard over the pulmonary fields, but breath sounds came through well and there was no impairment of resonance. The abdomen was not distended, and no abdominal organs or masses were palpable. A small umbilical hernia was present.

Ten days after admission, diarrhea developed which was temporarily controlled by restriction of diet but later recurred, and was associated with large, foul gray stools, abdominal distention and failure to gain weight. Duodenal drainage revealed normal amylase content, but low trypsin activity. Stool fat varied from 12 to 17 per cent of the dry weight. The glucose tolerance curve was flat. A vitamin A absorption test showed a flat curve when percomorph liver oil was administered, but a normal rise when vitamin A was administered in aqueous dispersion. A gastrointestinal series showed delayed passage of barium through the small bowel and several irregularly dilated loops of small bowel, with segmentation and alteration of the mucosal pattern, suggestive of either celiac disease or cystic fibrosis of the pancreas. Roentgenograms of the chest showed persistence of an atelectatic area at the base of the right lung, with overaeration of the remaining pulmonary fields. The baby was placed on a "nutramigen" formula and given an aqueous dispersion of vitamins. On this regimen, he showed gradual gain in weight and reduction in the number and size of stools, and he was discharged improved on the one hundred and tenth hospital day.

METHOD OF ESTIMATION OF VITAMIN A

The method employed for the estimation of vitamin A is a modification of that described by May and his colleagues.[2] One cubic centimeter of serum was treated with 1 cc. of ethyl alcohol to free the vitamin A from protein, and was then extracted with 2 cc. of redistilled petroleum ether (boiling point, 35 to 60 C.) by shaking for ten minutes. The tubes were centrifuged at low speed for thirty seconds to break up the emulsion. The layer of petroleum ether was transferred by aspiration to another test tube as completely as possible. The serum was extracted again with another 2 cc. of petroleum ether, the second extract being added to the first. Further extractions were found to be unnecessary. A pinch of anhydrous sodium sulfate was added and the tube gently shaken.

The petroleum ether extracted was transferred to a cuvette as quantitatively as possible without getting over any of the sodium sulfate, and the volume adjusted to 4 cc. with petroleum ether. The light transmission at 440 millimicrons was measured in a Coleman universal spectrophotometer. The carotene value was read from a calibration curve obtained by plotting 0.5 to 10 micrograms of carotene against percentage of transmission on semilogarithmic paper.

The contents of the cuvette were transferred quantitatively to another cuvette and the tube set in a warm water bath not over 50 C. The solution was evaporated to dryness by gently passing a stream of nitrogen over the solution. To the dry residue was added 1.0 cc. of chloroform, and the cuvette was shaken gently to effect solution.

The instrument was set at 100 per cent transmission at 615 microns with the blank which was freshly prepared by adding to a cuvette, matched with the one containing the specimen being analyzed, 1 cc. of chloroform and 3 cc. of antimony

trichloride reagent. With an extremely fast delivering pipette, 3 cc. of antimony trichloride reagent was added to the specimen cuvette which was quickly shifted into the path of the light without passing the instrument. The percentage of transmission was read at maximum deflection of the galvanometer which occurred within four to five seconds. The apparent vitamin A content was read from a calibration chart obtained by plotting 0.3 to 3.0 micrograms of vitamin A against percentage of transmission on semilogarithmic paper. Since carotene interferes in the estimation of vitamin A in that 100 micrograms of carotene gives the same absorption with antimony trichloride at 615 millimicrons as does 5.6 micrograms of vitamin A, the true vitamin A value was obtained by subtracting the vitamin A equivalent of the carotene content from the apparent vitamin A content.

The mean values and standard deviations of known amounts of vitamin A recovered from the petroleum ether extract of 1 cc. of serum are recorded below. The recovery studies were carried out by performing the first extraction with the vitamin A standard in petroleum ether.

TABLE 5.—*Mean Values and Standard Deviations of Known Amounts of Vitamin A Recovered from Petroleum Ether Extract of One Cubic Centimeter of Serum*

Number of Determinations	Vitamin A Added, Micrograms	Mean Amount Recovered, Micrograms	Average Deviation from Mean, Micrograms	Standard Deviation of Mean, Micrograms
30	0.560	0.530	±0.0360	±0.0424

SUMMARY

Various means of increasing the vitamin A level in the serum of normal children as well as in those with impaired absorption were studied.

Intramuscular injection of an aqueous dispersion of vitamin A resulted in a moderate rise in the serum level of vitamin A, in contrast to that reported on the intramuscular injection of fish liver oil, whereby no significant rise was obtained.

Absorption of vitamin A, as measured by vitamin A tolerance curves in blood serum, was far better with an aqueous dispersion of fish liver oil than with fish liver oil itself. This was true in children with either impaired or unimpaired intestinal absorption.

An aqueous dispersion of fish liver oil alone resulted in a greater absorption of vitamin A than did an aqueous dispersion of fish liver oil supplemented with vitamins B and C.

A solution of the dispersing agent, alone, produced no rise in the concentration of vitamin A in the serum.

It is concluded that vitamin A in fish liver oil is more easily absorbed from an aqueous dispersion than from the pure fish oil itself.

Dr. S. M. Gordon, of Endo Products, Inc., prepared and supplied the various aqueous dispersions of vitamin A used in this study. Mead Johnson and Company provided the percomorph liver oil used.

FREQUENCY OF ENCEPHALITIS AS A COMPLICATION OF MEASLES

Report of Twenty Cases

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AND
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ALTHOUGH sporadic reports of measles encephalitis are found in the literature prior to the year 1923, it is only in the last two decades that encephalitis as a complication of measles has seemed to occur in epidemic proportions. It is difficult to determine the exact incidence of this condition, as not all cases of measles are reported and many cases of mild encephalitis may be missed. Stimson [1] stated the opinion that this complication usually develops in less than 1 per thousand cases.

TABLE 1.—*Incidence of Encephalitis Complicating Measles* [2]

Author and Year	Cases of Measles	Cases of Encephalitis	Rate
Top, 1937-1938, Detroit	30,000	2	1:15,000
Gunn and Russel, 1935-1936, London	13,156	5	1:2,600
Peterman and Fox, 1931, Milwaukee	15,001	13	1:1,150
Hoyne, 1938, Chicago	37,831	32	1:1,300
Peterman and Fox, 1938, Milwaukee	27,081	14	1:1,900
New York, 1941	79,637	60	1:1,300
Hoyne and Slotkowski, 1946, Chicago	12,846*	20	1:642

* This figure (January to June), provided by the Chicago Health Department, has been added to the original table.

Table 1 [2] discloses the incidence in previously reported epidemics of measles and also in our series. There were 10 additional cases at another contagious disease hospital which are not included.

From January through June of 1946, 307 patients were admitted to the Cook County Contagious Hospital with the diagnosis of measles. Table 2 divides these cases into three separate age groups, showing the number of cases of measles encephalitis in each particular group and the relationship to other complications.

From the Cook County Contagious Disease Hospital.

1. Stimson, P. M.: Common Contagious Diseases, ed. 3, Philadelphia, Lea & Febiger, 1940.

2. Litvak, A. M.; Sands, I. J., and Gibel, H.: Encephalitis Complicating Measles, Am. J. Dis. Child. **65**:265 (Feb.) 1943.

Table 2 provides the following information:

1. Twenty of the 307 cases were diagnosed as measles encephalitis (6.5 per cent).
2. One hundred and seventy-two patients were under 5 years of age, with 6 instances of encephalitis (3.5 per cent).
3. One hundred and one patients were in the age group of 5 to 15, with 12 cases of encephalitis (12 per cent).
4. Thirty-four patients were over 15 years of age, and 2 of these had encephalitis (6 per cent).
5. Although Negroes constituted more than one fourth of the total admissions, all instances of measles encephalitis were among white patients.

Careful analysis of these 20 cases revealed nothing characteristic which would explain the cause of this complication. Our observations

TABLE 2.—*Analysis of Measles Admissions in Separate Age Groups*

Reason for Hospitalization	Under 5			5 to 15			Above 15			Total			
	W*	N†	No.	W*	N†	No.	W*	N†	No.	W*	N†	No.	%
Bronchopneumonia...	60	18	78	20	8	28	2	4	6	82	30	112	36.4
Otitis media.....	10	4	14	4	1	5	0	0	0	14	5	19	6.1
Encephalitis.....	6	0	6	12	0	12	2	0	2	20	0	20	6.5
Social problems, etc...	48	26	74	43	13	56	12	14	26	103	53	156	51.0
Total.....	124	48	172	79	22	101	16	18	34	219	88	307	

* White. † Negro.

led us to believe that the intensity of the eruption was of no significance in anticipating the possibility of encephalitis. We found that encephalitis occurred as a complication in patients with a comparatively mild-appearing attack of the disease as well as among those in whom the infection was of an intensive character. Carithers [3] mentioned the theories advanced, and these include "(1) the invasion of the central nervous system by the virus of measles, (2) the invasion of the central nervous system by a neurotropic strain of this virus, (3) an allergic reaction within the central nervous system to this virus and (4) infection with a virus separate and distinct from the virus of measles." In addition, we believe that there may be a constitutional tendency for the cortex to be more vulnerable than usual, and that, when combined with precipitating factors, neurologic manifestations make their appearance.

Clemens [4] reported a case of premeasles encephalitis with neurologic manifestations arising eleven days before the appearance of the typical

3. Carithers, H. A., Jr.: Encephalitis Complicating Measles, J. Florida M. A. **29**:324 (Jan.) 1943.

4. Clemens, H. H.: Premeasles Encephalitis, J. Pediat. **22**:731 (June) 1943.

exanthem. In our series there was 1 instance in which the onset of encephalitis occurred one day prior to the appearance of the eruption. One of us [5] had a similar case in 1938. Hamilton [6] reviewed 241 cases and found the average time elapsed after appearance of the rash before the onset of encephalitic symptoms was five and two-tenths days as compared with two and seven-tenths days in his own series of 44 cases. Our average, when the single instance in which encephalitis developed prior to the eruption is excluded, was three and four-tenths days. We did not observe any case in which encephalitis followed a complete subsidence of the eruption. These facts in themselves suggest that the term "postmeasles" encephalitis, although frequently used, is misleading.

There was considerable variability in the initial symptoms of encephalitis. The types of onset may be divided into two groups: (1) abrupt, convulsions being the presenting manifestation of irritation of the central nervous system, and (2) gradual, with a change in the mental condition varying from lethargy to extreme irritability, with or without convulsions. In 9 of the 20 patients, including a 20 year old woman, there was a history of at least one convulsion prior to admission. A 15 year old girl had convulsions after entering the hospital.

Neurologic findings on physical examination were as variable as symptoms at the onset. Meningeal irritation was manifested in some by nuchal rigidity and positive Kernig and Brudzinski signs. Reflexes were either hypoactive or hyperactive, normal or absent completely. Although paralysis of extremities was not ordinarily observed, 1 patient did experience paralysis of the lower extremities but eventually regained fully the use of both legs.

Temperature peaks attained by different patients varied considerably. Usually in the course of the illness there was pronounced pyrexia. The highest temperature recorded was 107.4 F. In this particular instance we learned that the patient, removed from the hospital prior to recovery, failed to survive. In another case a boy with a temperature of 107 F. eventually made a remarkable recovery. Although this patient was practically comatose for several weeks, his mental condition appeared to be normal when he was discharged from the hospital.

Lumbar puncture was performed in 16 of the 20 cases. The findings are analyzed in table 3. It may be added that a high cell count and a pronounced elevation in spinal fluid protein is not necessarily a poor prognostic sign. One patient with pleocytosis (400 cells) and a protein level of 530 mg. made a complete recovery.

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5. Hoyne, A. L.: Measles in 1938: Analysis of Four Hundred Cases with Twenty-Fight Instances of Encephalitis, Illinois M. J. **76**:136 (Aug.) 1939.

6. Hamilton, P. M., and Hanna, R. J.: Encephalitis Complicating Measles: A Report on Two Hundred and Forty-One Cases Collected from the Literature and on Forty-Four Additional Cases, Am. J. Dis. Child. **61**:483 (March) 1941.

In several instances convulsions were present when patients were admitted. The convulsions were controlled with a few drops of chloroform on a mask. To prevent a recurrence, one of the barbiturates was given either per rectum as a retention enema (sodium pentobarbital) or by parenteral injection (sodium phenobarbital). Oxygen was used in the presence of dyspnea, tachypnea or cyanosis.

As a rule a lumbar puncture was performed in the examining room, but when the patient was considered too ill this procedure was deferred.

No fast and rigid rule was followed in respect to giving fluids parenterally. Manifestation of increased intracranial pressure, turgor of the tissues and other signs of hydration were the criteria which determined the type and volume of fluid administered.

TABLE 3.—*Summary of Data on Spinal Fluid*

Number	Appearance	Pandy Reaction	Cells	Protein, Mg./100 Cc.	Glucose, Mg./100 Cc.	Culture
1	Clear and colorless	0	0	40	120	No growth or contaminated
2	Clear and colorless	1+	100	30	59	No growth or contaminated
3	Clear and colorless	0	36	49	72	No growth or contaminated
4	Clear and colorless	2+	400	530	54	No growth or contaminated
5	Clear and colorless	0	18	64	80	No growth or contaminated
6	Clear and colorless	0	9	49	67	No growth or contaminated
7	Clear and colorless	0	198	200	59	No growth or contaminated
8	Clear and colorless	0	10	45	101	No growth or contaminated
9	Clear and colorless	1+	12	74	106	No growth or contaminated
10	Clear and colorless	1+	250	184	85	No growth or contaminated
11	Clear and colorless	1+	360	...	..	No growth or contaminated
12	Clear and colorless	0	80	...	..	No growth or contaminated
13	Clear and colorless	0	10	...	..	No growth or contaminated
14	Clear and colorless	0	7	64	82	No growth or contaminated
15	Clear and colorless	2+	90	175	59	No growth or contaminated
16	Clear and colorless	0	0	35	105	No growth or contaminated

Measles convalescent serum in dosages varying from 20 to 100 cc. was administered intravenously to 7 patients. In 1 instance 40 cc. of gamma globulin was given to a patient whose condition was critical, but we were unable to decide that this treatment had any beneficial effect. Our opinion was the same in respect to measles convalescent serum when used for treatment of encephalitis. Pooled plasma, which is more readily available, was used liberally and repeatedly in almost all instances. The total volume of plasma injected during the acute stage varied from 250 to 1,250 cc., depending on the severity of the encephalitis. Whole blood, typed and cross matched, was given whenever indicated.

In 3 instances in which the patients remained in a semicomatose condition for more than a week and had a loss of deglutition, tube feedings were instituted and consisted of a dietene-high mixture of protein milk and amigen. In these cases total protein and albumin-globulin ratio were determined periodically and amino acids were employed parenterally in the presence of hypoproteinemia. Vitamins were administered empirically.

Occasionally a well padded cast was placed on a spastic extremity to prevent a contracture deformity and later physical therapy was employed to restore complete muscular function.

At the time of admission it was difficult, if not impossible, to prognosticate in regard to the chances for recovery. Hyperpyrexia and convulsions during the acute stage or even persistence of a semicomatose condition for several weeks was not always associated with a fatal outcome or even permanent damage to the nervous system. In 1 instance the patient remained in a comatose condition for a month, yet made a complete recovery.

Of the 20 patients with encephalitis 2 died shortly after admission, having been in the hospital less than twenty-four hours. In each of these fatal cases the children were 3½ years of age. Another patient, a 15 year old girl, died after being transferred to a private hospital. Including the latter, this gives our series a fatality rate of 15 per cent. Of the remaining 17 patients 16 made a complete recovery, and no mental complications have been noted after a period of one month. One patient, a 2 year old boy, still had some muscular spasticity and incoordination at the time he left the hospital. No further information has been received concerning his progress. The number of hospital days per patient varied from six to fifty with an average of sixten and one-half days.

COMMENT

Encephalitis is an early complication and rarely occurs after the rash of measles has disappeared. In respect to age it is much commoner after 5 years than before. Negroes are likely to escape this complication almost entirely.

Even in cases of extremely severe attacks complete mental as well as physical recovery is possible. Our fatality rate for this series was only 15 per cent. This is in sharp contrast to a previous report by one of us (A. L. H.), in which there was a fatality rate of more than double that figure and approximately one third of the survivors had mental or physical defects.

It seems apparent that measles encephalitis is becoming more frequent. Our series of 20 makes a ratio of 1 to 642 on the basis of cases of measles reported in Chicago. Moreover, if we include 10 additional cases, 3 of which were fatal, observed by one of us at Municipal Contagious Hospital, then the ratio for 30 patients with encephalitis becomes 1 per 428 reported cases of measles. We believe this to be the highest incidence for measles encephalitis that has been reported.

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GLYCOGEN CONTENT OF ISOLATED WHITE BLOOD CELLS IN GLYCOGEN STORAGE DISEASE

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GLYCOGEN storage disease (von Gierke's disease) is a rare condition in childhood, and little is known about its pathologic chemistry. In a recent study on 2 cases of glycogen storage disease Bridge and Holt [1] called attention to the glycogen content of whole blood. The occurrence of an increase in the level of glycogen in the blood had been reported by previous investigators.[2] Bridge and Holt identified the polysaccharid present in blood of glycogen storage disease as glycogen by its chemical properties. Since 97 per cent of the total glycogen has been found in the blood cells, they calculated from whole blood glycogen a concentration of from 6 to 10 per cent of this carbohydrate in the white blood cells. The assumption was made that all the glycogen is concentrated in the leukocytes with none in the erythrocytes.

The present study deals with direct glycogen determinations on isolated white blood cells in the hepatic form of glycogen storage disease. Determinations on whole blood, plasma and packed red blood cells are also included.

REPORT OF A CASE

First Admission.—The patient, a boy, was 5 months old when first examined. The family history was not contributory. The patient was born prematurely; his birth weight was 3 pounds, 12 ounces (1,647 Gm.). Gain in weight had been slow. He weighed 9 pounds, 11 ounces (4,394 Gm.) at 4 months and 10 pounds, 5 ounces (4,678 Gm.) at 5 months. He slept most of the time. He tended to be constipated, with hard yellow stools. He had vomited during the previous three days. On physical examination there was some pallor of the mucous membranes, and subcutaneous tissue was sparse. His length was 24 inches (61 cm.); his trunk, 8¼ inches (21 cm.); his legs, 10½ inches (26.7 cm.); his width of chest, 5½ inches (14 cm.); his width of hip, 4½ inches (11.43 cm.), and the circumference of his head, 15½ inches (39.4 cm.). A loud blowing systolic murmur was heard over the entire chest, front and back. No enlargement of the heart was noted on percussion. The liver was unusually large, extending down to the

This study was aided by a grant from Mead, Johnson and Company, Evansville, Ind.

From the Boston Floating Hospital and the Department of Pediatrics, Tufts College Medical School.

1. Bridge, E. M., and Holt, L. E.: J. Pediat. **27**:299, 1945.

2. van Creveld, S.: Arch. Dis. Childhood **9**:9, 1934. Unshelm, E.: Ztschr. f. d. ges. exper. Med. **96**:129, 1935. Ellis, R. W. B., and Payne, W. W.: Quart. J. Med. **5**:3, 1936.

crest of the ilium on the right. The lower margin was smooth and extended from the midcostal area on the left to the right iliac crest. The spleen was palpable below the left costal margin. After withdrawal of food acetone breath was noted. Clinical impression was that the infant had glycogen storage disease (hepatic form) and probable congenital heart disorder.

Laboratory Data: Roentgen examination showed the heart to be normal in size and shape.

There were 4,135,000 red blood cells per cubic millimeter, with 12.6 Gm. of hemoglobin per hundred cubic centimeters (81 per cent), and (1) 16,500 white blood cells with 4 per cent adult polymorphonuclear cells, 95 per cent lymphocytes and 1 per cent monocytes and (2) 9,600 white blood cells with 14 per cent adult polymorphonuclear cells, 85 per cent lymphocytes and 1 per cent monocytes.

The urine contained acetone but no albumin or sugar. The Hinton, Wassermann and Kahn reactions were negative. The fasting level of blood sugars was 35 mg. per hundred cubic centimeters and the levels after feeding at 10:15 and 11:15 a. m. were 52 and 72 mg., respectively. There was 520 mg. of serum cholesterol per hundred cubic centimeters.

Readmission at the Age of 11 Months.—The infant had intermittent periods of fever due to respiratory infection. There was slight progress in development; the infant's weight was 11 pounds, 2 ounces (4,946 Gm.) and his length was 25½ inches (64.8 cm.). The liver had increased in size; the left lobe extended far into the left hypochondrium.

The glucose tolerance test showed no glycosuria. The fasting level of glucose was 40 mg. per hundred cubic centimeters; the level after one-half hour was 176 mg.; after one hour, 120 mg.; after two hours, 100 mg., and after three hours, 20 mg.

The galactose tolerance test (10 Gm. of galactose was administered orally) showed no galactosuria. The fasting level of galactose was 10 mg. per hundred cubic centimeters; the level after five minutes was 24 mg.; after fifteen minutes, 38 mg; after thirty minutes, 44 mg.; after sixty minutes, 29 mg., and after one hundred and twenty minutes, 15 mg.

The serum cholesterol level was 304 mg. per hundred cubic centimeters.

There were 2,980,000 red blood cells per cubic millimeter, with 10.1 Gm. of hemoglobin per hundred cubic centimeters (65 per cent), and 8,900 white blood cells, with 27 per cent adult polymorphonuclear cells (4 per cent band forms), 69 per cent lymphocytes, 3 per cent monocytes and 1 per cent blast forms.

Analysis of the blood of the patient[3] demonstrated that 1 cc. did not contain detectable amounts of glucophosphomutase.[4]

On two readmissions at the age of 14 and 21 months respectively, both times because of respiratory infections, no essential change of the physical findings was noted. The height at 14 months was 26 inches (66 cm.). There was no progress in development. The fasting level of blood sugar was 32 mg. per hundred cubic centimeters.

At the present time the child is 3 years old and shows gradual progress in development. The size of the liver is unchanged.

Since the diagnosis of glycogen storage disease seemed to be well established, neither an epinephrine tolerance test nor a liver biopsy

3. This analysis was carried out by Dr. Gerhard Schmidt.

4. Determinations on biopsy specimens from the liver might be more contributory.

were carried out. The results of glycogen determinations on whole blood and its different constituents will be reported in detail. They are of some diagnostic value, since in general there are no other diseases with glycogen values of the same order of magnitude except chronic myelogenous leukemia and polycythemia.[5] They are also of general interest as a study of the reaction of the white blood cells under pathologic conditions.

TECHNIC

The method of determining glycogen in blood and isolated white blood cells has been described in previous studies.[6] It is essentially a micromodification of the Pflüger[7] method. A few deviations are made from the procedures applied by previous investigators. The acid hydrolyzates of the alcohol precipitates of whole blood as well as of the blood cells are subjected to yeast fermentation in order to determine nonsugar-reducing substances, since determinations of whole blood glycogen without yeast fermentation result in erroneously high values. The fermentation is carried out at a p_H of 4 to 6, a 1 per cent solution of potassium dihydrogen phosphate being used as a buffer. The Somogyi[8] method is used exclusively to determine the glucose in the hydrolyzates, since the copper reagent is more specific than the ferricyanide of other reductometric methods.

The glycogen determination in whole blood is carried out on 1 cc.; that in plasma on 2 cc. The results are recorded in milligrams of glucose per hundred cubic centimeters. The leukocytes are isolated from 12 cc. of blood in a Cushman[9] tube. The layer of white blood cells is analytically weighed, and the cells are counted in a dilution of 1 to 100. The results are recorded in micrograms per million white blood cells. The red blood cells are collected from the lower bulb of the Cushman tube and counted in a dilution of 1 to 1,000. The analysis is carried out on 180 to 200 mg. of packed red blood cells, and the results are recorded in micrograms per million cells. The purity of the cell layers was verified microscopically. An admixture of a small remainder of blood platelets does not interfere with the quantitative yield of glycogen in white blood cells, if the Somogyi method is used. It was shown[6] that the ribonucleic acid content of blood platelets explains at least a large part of the reduction obtained after acid hydrolysis. In no instance could glycogen be demonstrated in the red blood cells.

RESULTS

In table 1 the results of glyocen determinations in whole blood, plasma, isolated white blood cells and the packed red cells are shown. All analyses were carried out under fasting conditions.

COMMENT

The glycogen values found in glycogen storage disease are considerably elevated above the average level in normal human blood (5.5 mg.

5. Wagner, R.: Blood **2**:235, 1947.
6. (*a*) Wagner;[5] (*b*) Arch. Biochem. **11**:249, 1946.
7. Pflüger, E.: Arch. f. d. ges. Physiol. **96**:1, 1903.
8. Somogyi, M.: J. Biol. Chem. **117**:771, 1927.
9. Butler, A. M., and Cushman, M.: J. Clin. Investigation **19**:459, 1940.

per hundred cubic centimeters). However, only exceedingly high levels are of diagnostic importance, since in the control material values similar to the lower values in glycogen storage disease were occasionally encountered. There are other conditions with hepatomegaly in childhood which may simulate glycogen storage disease. Furthermore, glycogen determinations in whole blood are not satisfactory technically because of the interference of nonsugar-reducing substances.

More exact information can be obtained from glycogen determinations on isolated leukocytes. Here the glycogen is concentrated and can be determined with the same degree of precision as in liver or muscle. There is no other condition known where the glycogen concentration in the white blood cells reaches high levels similar to those in glycogen storage disease. It was shown in previous studies [5] that the granulated white blood cell is the only carrier of glycogen in normal blood. Neither lymphocytes nor blast cells contain measurable amounts

TABLE 1.—*Glycogen Content of Whole Blood, Plasma and Leukocytes in Glycogen Storage Disease*

Date	No. of Experiments	Leukocytes per Cu. Mm.	Adult Poly., per Cent	Whole Blood Glycogen, Mg. per 100 Cc.	Plasma Glycogen, Mg. per 100 Cc.	Glycogen per Million R.B.C., γ	Glycogen per Million Total W.B.C., γ	Glycogen per Million Adult Poly., γ	Glycogen Concentration* in Adult Poly., per Cent
2/10/44	108	16,500	4.0	25.8	....	0.00	1.25	31.3	3.80
2/14/44	109	9,600	14.0	47.7	8.7	0.00	3.14	22.4	2.73
8/ 4/44	138	8,900	26.0	31.9	10.0	0.00	4.89	18.8	2.29
8/14/44	139	9,300	22.0	27.4	15.6	0.00	2.48	11.3	1.37
6/18/45	171	11,600	20.0	33.8	....	0.00	5.03	25.2	3.07

* This is calculated on the assumption that the nitrogen and water content in human leukocytes is the same as in those of rabbits. The values are obtained by dividing the glycogen content per million adult polymorphonuclear cells by 8.2.[5]

of this polysaccharid. The same holds for red blood cells and for plasma in normal conditions. The glycogen content per million normal total white blood cells is 2.54 micrograms. Assuming 60 per cent granulated leukocytes in normal blood, the average of the glycogen content per million normal granulated white blood cells is 4.23 micrograms. Even in chronic myelogenous leukemia with the highest glycogen levels ever observed in whole blood the individual leukocyte does not contain more glycogen than the normal cell. Only in polycythemia were higher concentrations of glycogen in the granulated white blood cells detected, but never as high as in glycogen storage disease. As shown in table 1, the range of glycogen per million adult polymorphonuclear leukocytes in glycogen storage disease is from 11.3 to 31.3 micrograms; that is, 2.7 to 7.4 times more than in normal leukocytes.

In experiments on rabbits a homogenous suspension of granulated leukocytes can easily be recovered from sterile peritoneal exudates

according to the method of de Haan.[10] In this cell material a glycogen concentration of 1.23 per cent was found. This is of the same order of magnitude as in the striated muscle. Assuming the same nitrogen and water content in human granulated leukocytes, a glycogen concentration of from 0.17 to 0.67 per cent can be calculated for normal wet human leukocytes.[5] The corresponding values in glycogen storage disease exceed the normal figures by a considerable amount (last column in table 1). A maximal concentration of 3.8 per cent was calculated.

In contrast to the plasma of normal persons, which was always found free of glycogen,[6b] the plasma in the present case contained 8.7 to 15.6 mg. per hundred cubic centimeters on three different occasions. This

TABLE 2.—*Glycogenemic Curve Following Intravenous Administration of 3 Gm. of Chemically Pure Glycogen in the Rabbit*

	Glycogen Content of Whole Blood, Mg. per 100 Cc.	Glycogen Content of Plasma, Mg. per 100 Cc.	Glycogen Content per Million Total W.B.C., γ	Glycogen Concentration* in the W.B.C., per Cent	Blood Sugar, Mg. per 100 Cc.
Fasting	7.6	0.0	1.36	0.17	96
After 10 minutes	350	258	....	....	...
After 30 minutes	283	208	7.9	0.96	264
After 60 minutes	238	...	....	....	202
After 120 minutes	139	102	....	....	193
After 180 minutes	95	...	....	....	182
After 240 minutes	61	...	....	....	194
After 300 minutes	48	...	....	....	...
After 360 minutes	39	...	....	....	...
After 420 minutes	32	7.0	....	....	...

* Glycogen content per million white blood cells

8.2

remarkable finding has its analogy in experiments carried out in the rabbit. After intravenous administration of 3 Gm. of chemically pure glycogen (15 cc. of a 20 per cent solution), in accordance with the technic of Morris,[11] a glycogenemic curve was obtained with a considerable part of the glycogen present in the plasma (table 2). Over 70 per cent of the injected glycogen could be recovered from the plasma up to two hours. After seven hours both whole blood and plasma still contained glycogen exceeding the fasting level by a considerable amount. The glycogen concentration in the white blood cells also showed a remarkable rise. After thirty minutes it was about six times higher than in fasting conditions. This finding is regarded as evidence of phagocytic action of the leukocytes toward glycogen.

10. de Haan: Arch. néerl. de physiol. **2**:674, 1918; cited by Abderhalden, E.: Handbuch der biologischen Arbeitsmethoden, Vienna, Urban & Schwarzenberg, 1927, vol. 4, pt. 4, p. 965.

11. Morris, D. L.: J. Biol. Chem. **148**:699, 1943.

It is not known whether glycogen usually is present in plasma in glycogen storage disease. However, from the experiment in the rabbit it may be concluded that at least part of the glycogen remains in the plasma. This may be a quantitative problem, depending on one hand on the total amount of glycogen in the blood stream, and on the other on the ability of the leukocytes to deal with the surplus glycogen.

The question arises whether the increased concentration of glycogen in the leukocytes in glycogen storage disease is the result of phagocytosis and storage or an inherent peculiarity of the enzymatic activity of these cells. There is more in favor of the latter hypothesis. As Bridge and Holt [1] have recently pointed out, glycogen storage disease is rather to be considered a developmental defect involving the enzyme system of specific organs than a primary metabolic disease. The granulated white blood cells represent one of the organs where an accumulation of glycogen occurs, exactly as in liver, kidney, heart, peripheral muscle and brain. From the experiments of Willstätter and Rohdewald [12] on the enzymes of leukocytes there is some evidence that the granulated leukocyte is incorporated in the system of tissues serving the carbohydrate metabolism.

From the diagnostic viewpoint glycogen determinations on isolated leukocytes in glycogen storage disease are superior to determinations in whole blood and seem to be as reliable as the study of biopsy specimens obtained from the liver. In the leukocytes of polycythemic blood elevated glycogen levels were encountered, but never in the same degree as in glycogen storage disease.[5] Moreover, these two conditions should not be confused. In other forms of hepatomegaly the glycogen content of the leukocytes was within normal limits.

SUMMARY AND CONCLUSIONS

The glycogen concentration in isolated leukocytes was determined in a case of the hepatic form of glycogen storage disease by a direct method. It is 2.7 to 7.4 times higher than in normal leukocytes, the maximal concentration amounting to 3.8 per cent. Glycogen could also be recovered from plasma. This chemical procedure may be used as a diagnostic test in cases in which glycogen storage disease is suspected.

12. Willstätter, R., and Rohdewald, M.: Ztschr. f. physiol. Chem. **247**:115, 1937.

SULFONAMIDE DRUGS

A Comparison of Blood Levels Obtained with Their Administration by Different Routes in Children

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IN 1942, Jorgensen and Greely [1] demonstrated that sulfadiazine can be administered subcutaneously in a 5 per cent aqueous solution without deleterious local effects. Since then others [2] have used this method of administration with some variations regarding dosage and interval between injections but, in general, following the plan which has been widely adopted for oral administration of the drug, namely, 50 to 75 mg. per kilogram (1/3 to 1/2 grain per pound) of body weight as an initial dose, and approximately twice this amount per day divided into three, four or six doses.[3] Glaser and Lawrence [2c] reported studies of the levels obtained in the blood when the drug was administered by the subcutaneous route. Aside from this study, little attention has been given to the pediatric aspects of subcutaneous administration of sulfonamide drugs. The following report presents the results of a study of blood levels obtained in children of different ages following the use of sulfadiazine according to several therapeutic routines.

PROCEDURES

Fifty-six children, ranging in age from 2 months to 12 years, have been studied. Some of these were receiving sulfadiazine because of infections; others were convalescent and received the drug for experimental purposes. Since the presence of infection does not appreciably affect the blood level obtained by a standard dose, children both with and without infections were included in the study. The dosage followed was that commonly used for oral administration, namely, 0.075 Gm. per

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1. Jorgensen, G. M., and Greely, D. M.: Subcutaneous Administration of Sodium Sulfadiazine, J. Pediat. **21**:325, 1942.

2. (*a*) Janeway, C. A.: The Use of Sulfonamides in the Treatment of Respiratory Infections in Children, New England J. Med. **229**:201-203, 1943. (*b*) Pratt, E. L.: Acute Bronchiolitis in Infants, M. Clin. North America **28**: 1098-1107, 1944. (*c*) Glaser, K., and Lawrence, G.: Subcutaneous Administration of Sodium Sulfadiazine, J. Pediat. **27**:492-496, 1945.

3. Logan, G.: The Use of Sulfonamides in the Treatment of Diseases of Infancy and Childhood, M. Clin. North America **28**:882-890, 1944.

kilogram of body weight (½ grain per pound) as an initial dose, with twice this amount for daily maintenance divided into four or six equal doses. The same schedule was followed for both oral and subcutaneous administration; in the latter case, the soluble sodium salt was used in a 5 per cent solution of distilled water. A high fluid intake was maintained but no alkalis were given. In several instances in which sulfanilamide was given intraperitoneally, different amounts, listed in a later section, were employed. Observations on blood levels were made on 0.1 cc. of capillary blood by a micromodification of the method of Marshall and Bratton.[4] Color comparisons were made with a Klett-Summerson photoelectric colorimeter.

TABLE 1.—*Average Blood Levels Obtained in Nine Children Following a Single Subcutaneous and a Single Oral Dose of Sulfadiazine—0.075 Gm. per Kilogram of Body Weight (½ Grain per Pound)*

5% Sodium Sulfadiazine Given Subcutaneously		Sulfadiazine Given Orally	
Interval, Hours	Blood Level, Mg.	Interval, Hours	Blood Level, Mg.
½	8.4	½	0.5
1	10.1	1	2.5
2	13.7	2	3.9
3	11.5	3	5.4
4	10.2	4	5.8
5	8.5	5	6.9
6	7.5	6	6.7
7	6.9	7	6.1
8	5.9	8	5.4
9	5.6	9	5.1
10	5.0	10	4.8
11	5.3	11	4.3
12	5.1	12	3.8

COMPARISON OF ORAL AND SUBCUTANEOUS ROUTES OF ADMINISTRATION

In order to compare the relative merits of the oral and subcutaneous routes of administration of sulfadiazine, a group of 9 children was given a dose of 0.075 Gm. per kilogram of body weight (½ grain per pound) as a single dose subcutaneously, and five days later the same amount was given orally. Blood levels of the drug were followed hourly for twelve hours. The results are shown in table 1. It will be seen that rise in blood level was much slower when the drug was given by mouth, the peak being reached only after five hours. Subcutaneous administration resulted in a satisfactory therapeutic level within one-half hour and a maximal concentration at two hours which was nearly twice that reached by the oral dose. Throughout the twelve

4. Marshall, E. K., and Bratton, C.: A New Coupling Component for Sulfanilamide Determination, J. Biol. Chem. **128**:537-550, 1939.

hours of observation, higher blood levels were maintained after subcutaneous than after the oral route of administration.

The blood levels maintained when 0.15 Gm. per kilogram (1 grain per pound) was given in four divided doses during each twenty-four

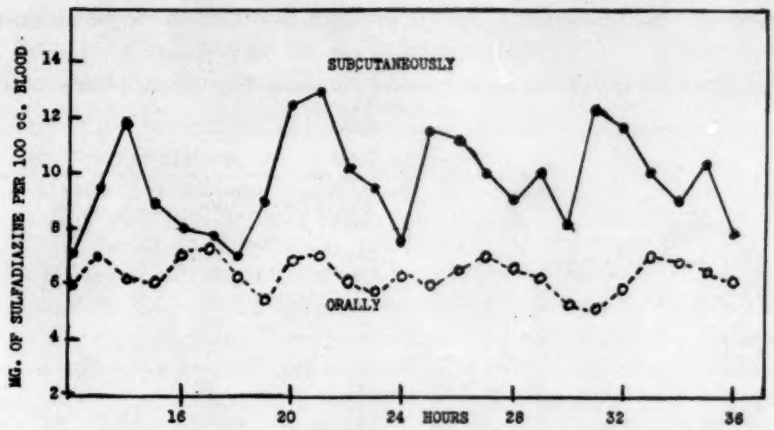

Chart 1.—Average blood levels obtained in a group of 14 children after oral and subcutaneous administration of sulfadiazine in doses of 0.15 Gm. per kilogram (1 grain per pound). The total amount for the day was divided into four equal doses and given at six hour intervals.

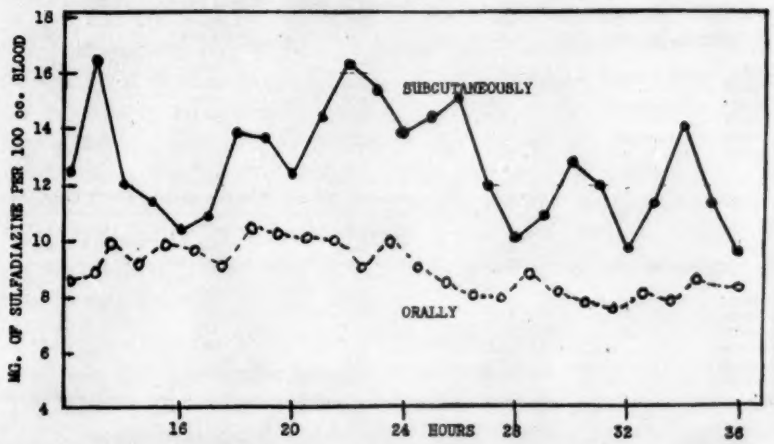

Chart 2.—Average blood levels obtained in a group of 14 children after oral and subcutaneous administration of sulfadiazine in doses of 0.15 Gm. per kilogram (1 grain per pound). The total amount for the day was divided into six equal doses and given at four hour intervals.

hour period were also studied. Charts 1 and 2 present the averages observed in four groups of 14 children, one group receiving the drug orally every four hours, one subcutaneously every four hours and the other two groups subcutaneously and orally, respectively, every six

hours for a period of fifty-four hours. While oral administration resulted in slightly lower and more stable blood levels, the fluctuations caused by the more rapid absorption of the drug administered subcutaneously were still within the range of satisfactory and safe therapy.

When the drug was continued over a still longer period of time, there was no appreciable change in basic blood levels or response to

TABLE 2.—*Average Blood Levels Obtained Following Two Weeks' Administration of Sulfadiazine*

	Orally Every Six Hours		Orally Every Four Hours	
Interval, Days	Blood Levels, Mg., Case 1	Blood Levels, Mg., Case 2	Blood Levels, Mg., Case 3	Blood Levels, Mg., Case 4
1st day	9.9	10.2	11.0	10.7
2d day	9.0	9.1	10.6	11.5
3d day	8.5	9.5	10.2	9.8
4th day	9.3	8.2	10.8	10.2
5th day	7.5	8.7	10.1	11.1
6th day	8.1	8.3	10.7	10.5
7th day	8.5	8.9	10.2	10.2
8th day	7.3	8.3	10.7	10.8
9th day	7.5	8.7	8.6	11.3
10th day	7.5	9.1	10.9	10.5
11th day	7.8	8.5	11.5	10.8
12th day	7.5	8.2	10.5	11.1
13th day	7.6	8.3	10.3	10.7
14th day	7.4	8.1	10.8	10.3

	Orally Every Six Hours		Orally Every Four Hours	
Interval, Hours	Blood Levels, Mg., Case 1	Blood Levels, Mg., Case 2	Blood Levels, Mg., Case 3	Blood Levels, Mg., Case 4
1 hour	7.1	7.9	10.3	10.5
2 hours	7.8	8.3	10.5	10.8
3 hours	7.5	8.1	10.6	9.7
4 hours	7.9	8.5	10.1	9.8
5 hours	7.5	8.0		
6 hours	7.4	7.2		

	Subcutaneously Every Six Hours		Subcutaneously Every Four Hours	
Interval, Hours	Blood Levels, Mg., Case 1	Blood Levels, Mg., Case 2	Blood Levels, Mg., Case 3	Blood Levels, Mg., Case 4
1 hour	8.2	7.5	10.5	10.8
2 hours	11.3	10.5	13.2	12.5
3 hours	12.1	11.2	12.1	12.7
4 hours	11.2	12.1	10.1	10.9
5 hours	8.4	9.3		
6 hours	6.9	7.2		

individual doses. This is illustrated in table 2, which presents the blood levels obtained at a standard time each day just before the administration of one of the regular doses of the drug—0.15 Gm. per kilogram per day (1 grain per pound) given in four divided doses. At the end of a two week period blood levels were obtained following oral and subcutaneous administration of single doses. It will be seen that during the two week period blood levels were well maintained, and the response to single doses by both routes was essentially the same as in previously

untreated patients. There is, therefore, no reason to believe that in children long continued use of the drug alters its effect on the blood level.

The rate of disappearance of the drug from the blood after cessation of therapy was observed in 12 children. Only traces were detectable after thirty-two hours and none after forty-eight hours. This is in agreement with the observations of Peterson and others [5] on adults, who found less than 1 mg. per hundred cubic centimeters of blood twenty-four hours after discontinuance of sulfadiazine therapy.

THE FACTOR OF AGE

As Janney and Winters [6] have also pointed out, age does not appear to be a factor in determining the blood level obtained, provided that the dosage is calculated according to weight. While individual children showed considerable variation in the drug levels found in the blood after the standard therapeutic regimens, the averages for children under and over the age of 2 years were essentially the same. Weight alone appears to offer a satisfactory basis for calculating dosages.

INTRAPERITONEAL THERAPY WITH SULFONAMIDE DRUGS

In 4 children, observations were made on the blood levels reached following the implantation of sulfanilamide crystals intraperitoneally at surgical operations. The results are shown in chart 3. While the observations are too limited to permit final conclusions to be drawn, they suggest that doses of 0.15 to 0.30 Gm. per kilogram (1 to 2 grains per pound) given intraperitoneally will produce therapeutically effective blood levels. Whether or not this has advantages over the oral and subcutaneous routes of administration cannot be stated from these data. According to Gardiner [7] sulfanilamide crystals disappear from the peritoneal cavity in six to twenty-four hours. Jackson and Coller [8] expressed doubt that the local action remains effective longer than one to two hours.

COMMENT AND CONCLUSIONS

Since the subcutaneous administration of sodium sulfadiazine has been shown to excite almost no local reaction,[1] it has been widely used, especially in small children. When for some reason oral therapy

5. Peterson, O. L.; Strauss, E.; Taylor, E. H., and Finland, M.: Absorption, Distribution and Excretion of Sulfadiazine, Am. J. M. Sc. **201**:357-367, 1941.

6. Janney, F. R., and Winters, K. J.: Review of Use of Sulfadiazine in the Treatment of Children, Am. J. Dis. Child. **65**:702-711 (May) 1943.

7. Gardiner, R. H.: Intraperitoneal Chemotherapy, Brit. J. Surg. **32**:49-65, 1944.

8. Jackson, H. C., and Coller, F. A.: Uses of Sulfonamide in the Peritoneum: Experimental and Clinical Observations, J. A. M. A. **118**:194-200 (Jan. 17) 1942.

is contraindicated as a result of vomiting or refusal, subcutaneous administration of the drug is simpler and as effective as intravenous administration. A high blood level is produced almost as quickly and fluctuates less.[9] These advantages are particularly great when the patients are infants or small children. In moderately or severely acutely ill patients, the time saved in obtaining an effective level is great enough to warrant administration of the initial dose in this simple manner and then continuing the maintenance dose orally, if the patient will tolerate it in such a manner, or subcutaneously if he will not.

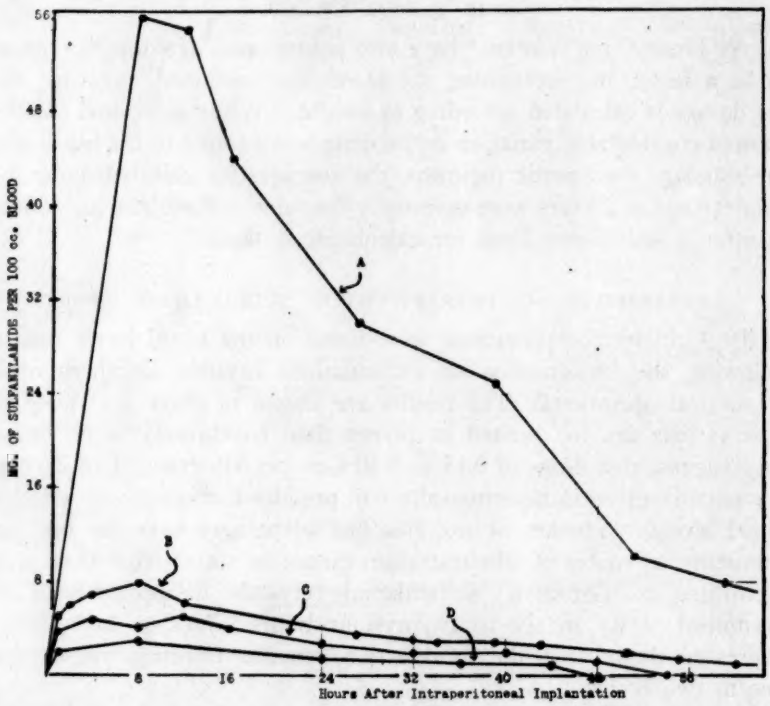

Chart 3.—Blood levels of sulfanilamide obtained in 4 children after intraperitoneal implantation of the drug in the amounts of 0.6 Gm. per kilogram (A), 0.15 Gm. (B), 0.3 Gm. (C) and 0.15 Gm. (D). Patient A was a 4 month old baby who had intussusception with gangrene and perforation of the intestine. Patients B and D were 11 and 8 year old children, respectively, who were operated on for perforated appendix. Patient C was a 7 month old infant with uncomplicated intussusception. In all cases sulfanilamide was placed in the peritoneal cavity at the time of operation.

9. (*a*) Wheeler, C., and Plummer, N.: Sulfadiazine and Sodium Sulfadiazine: A Comparison of Clinical and Pharmacologic Values, Ann. Int. Med. **16**:269-285, 1942. (*b*) Domm, A. H.; Flippin, H. F.: Schwartz, L., and Rheinhold, J. G.: Intravenous Use of Sodium Sulfadiazine in Treatment of Pneumococcic Pneumonia, Arch. Int. Med. **69**:51-57 (Jan.) 1942.

The average sulfonamide level obtained by giving the maintenance doses of sulfadiazine orally every four hours (9.9 ± 2.25) [10] corresponded closely to that resulting from administration of 5 per cent sodium sulfadiazine solution every six hours subcutaneously (9.6 ± 2.79).[10] Had the sodium salt also been used orally, the rate of absorption probably would have been more rapid.[11] However, since the sodium salt is not used orally in clinical practice, the comparison with the regular clinical routine was thought to be more valuable.

The variation in hourly levels obtained following subcutaneous administration of sulfadiazine was not so great as that following intravenous injection, but was greater than occurred after oral ingestion. Therefore, when following daily blood sulfonamide levels in a patient receiving sodium sulfadiazine subcutaneously, it is important that the sample be taken at the same time each day. If the blood levels are taken immediately before the next dose is given, the low maintenance point is obtained, and a better guide to adequacy of dosage results.

There is disagreement in the literature and among clinicians as to exactly what level is therapeutically effective without being severely toxic. However, most writers [12] agree that levels of 10 mg. per hundred cubic centimeters of blood are therapeutically effective against most of the susceptible organisms, and that above 10 mg. per hundred cubic centimeters toxic reactions are seen more commonly. Plummer and Wheeler [13] showed that in 1,155 cases there were 1.8 per cent reactions in those having levels of 5 mg. or less; 7.9 per cent reactions with levels of 5 to 10 mg.; 12.8 per cent reactions with levels of 10 to 15 mg., and 14 per cent reactions with levels over 15 mg. In the 56 children observed in the present study, there was one toxic reaction, which consisted in crystaluria which became evident fifty-three hours after subcutaneous administration of sodium sulfadiazine had been begun on a four hour schedule. Thus, from the experimental results, it can be concluded that when soluble sulfonamide drugs are given subcutaneously in the

10. Standard error of deviation from the mean.

11. (*a*) Status of Oral Use of Sodium Salts of Sulfonamides, report of the Council of Pharmacy and Chemistry, J. A. M. A. **121**:1008 (March 27) 1943. (*b*) Wheeler and Plummer.[9a]

12. Lowell, F. C.: Present Status of Sulfa Therapy, M. Clin. North America **27**:1247-1255, 1943. Trevett, G. I.; Nelson, R. H., and Long, P. H.: Sulfadiazine: Clinical Use in Bacterial Infections Other than Pneumonia, Bull. Johns Hopkins Hosp. **69**:303-313, 1941. Flippin, H. F.; Schwartz, L., and Domm, A. H.: Treatment of Pneumococci Pneumonia, J. A. M. A. **121**:230-237, (Jan. 23) 1943. Davis, B. D.: New Biologic Concepts Derived from Research on Sulpha Drugs, New England J. Med. **230**:734-739, 1944. Logan.[8]

13. Plummer, N., and Wheeler, C.: The Toxicity of Sulfadiazine: Observations on 1,357 Cases, Am. J. M. Sc. **207**:175-184, 1944.

doses recommended the blood levels obtained are therapeutically effective and toxic reactions are minimal.

SUMMARY

Fifty-six children have been studied to determine the relative merits of the oral and subcutaneous routes of administration of sulfonamide drugs.

Administration of sodium sulfadiazine as a 5 per cent solution in distilled water was found to be safe and to give somewhat higher levels in the blood with greater fluctuations between doses than the same dose given by mouth.

These levels could be maintained satisfactorily without change in dosage for at least two weeks.

Age does not appear to be a factor in determining the level of sulfadiazine obtained in the blood provided that the dose is calculated according to weight.

Four children in whom sulfanilamide was implanted intraperitoneally were observed. The results suggest that 0.15 to 0.30 Gm. per kilogram (1 to 2 grains per pound) give safe blood levels.

It is concluded that sulfadiazine administered subcutaneously can be relied on to give safe and satisfactory effects whenever oral administration cannot be used.

Case Reports

CONGENITAL DIAPHRAGMATIC HERNIA ON THE RIGHT INVOLVING THE ASCENDING PART OF THE COLON

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WHILE not unheard of, congenital diaphragmatic hernia on the right diagnosed in infancy is believed rare enough to warrant the report of a single case.

This child was observed by me at regular intervals from birth until the seventh month, at which time symptoms referable to the abnormality first developed.

HISTORY OF THE CASE

J. L. H. III was born Oct. 10, 1946, being the first child of a 17 year old mother. During the second month of gestation a positive Wassermann reaction had been obtained, and intensive antisyphilitic treatment was carried out during the entire pregnancy. At the time of delivery both the mother's Wassermann reaction and the Wassermann reaction of the cord were negative.

The infant breathed spontaneously at birth, and his color was good at all times. Breast feeding was supplemented with a Dryco formula.

At four weeks the infant's gain was insufficient and he seemed hungry. An SMA formula was given, and growth and development were satisfactory.

At 3 months the right side of the chest was observed to be larger than the left. Breath sounds were clear, however, and no roentgenologic study was made.

Except for a food rash which occurred when a canned milk formula was instituted and which cleared promptly on reverting to SMA, the infant's course was uneventful until April 27, 1946, when a cough remedy was requested by telephone. The following day the child was seen at home and appeared listless. The temperature was 100 F. (rectally). His back was slightly extended and his neck was rigid. He had vomited clear fluid all day and had refused his feedings. He had a harsh, rasping type of cough, and musical rales were heard in the right side of the chest.

He was hospitalized the same day, and a lumbar puncture was done, which was normal. The following day an anteroposterior roentgenogram of the chest was made which showed a mass in the right side of the thorax at first thought to represent a collapsed lobe of lung, probably a tension pneumothorax. Further roentgenologic studies showed the mass to be fairly constant in size and shape, and instead of growing worse, the baby appeared to feel normal again.

Barium meal and barium enema studies were then made,[1] which showed the mass to be the ascending part of the colon, the appendix and the terminal part of the ileum. Barium was forced with great difficulty through the diaphragmatic opening, and it was noted during his hospital course that cereals and other soft foods caused some vomiting and apparent discomfort, while on a strict liquid diet he did well.

1. The roentgenologic studies were made by Dr. E. D. Sellers.

Surgical repair was done through a transthoracic approach on May 22, 1946. The hernial opening was found at the medial lumbocostal arch. There was a complete hernial sac which was freed with some difficulty and resected. A satisfactory closure was effected, but postoperative shock developed about ten minutes after the operation was completed, and the patient did not regain consciousness in spite of blood plasma and stimulants.

202 Grape Street.

CONGENITAL ESSENTIAL THROMBOPENIC PURPURA

Report of the Condition in Fraternal Twins

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TO date, no case of congenital essential thrombopenic purpura in twins has been described in the literature, which contains reports on 19 cases. The literature up to 1936 was reviewed by Sanford, Leslie and Crane,[1] who listed 12 cases. Since then cases have been reported by Davidson,[2] Whitney and Barritt,[3] Urbanski and Hutner,[4] Schefrin and Schechtman[5] and Morrison and Samwick.[6] The latter proposed the following criteria for a diagnosis of thrombopenic purpura: (1) purpura, with petechiae and ecchymoses; (2) increase in bleeding time; (3) increase in clot retraction time; (4) decrease in platelets; (5) no change in coagulation time; (6) no change in prothrombin time; (7) either normal or increased number of megakaryocytes and/or immature megakaryocytes; (8) normal vitamin C content; (9) positive response to tourniquet test; (10) normal or slightly enlarged spleen; (11) absence of adenopathy; (12) leukemoid reaction with leukocytosis and polynucleosis, especially in the presence of active bleeding; (13) absence of lymphocytosis, especially in the presence of active bleeding, and (14) absence of leukopenia.

Schefrin and Schechtman stated that no report of a case of congenital thrombopenia has appeared in which the mother did not have thrombopenic purpura. The mother of their patient and the mother of the patient in the case to be reported did not have purpura, although the latter had an unequivocably diminished platelet count of 182,400. (The normal platelet count is 200,000 to 400,000.)

J. M., a boy, was one of full term dissimilar twins. His weight at birth was 2,682 Gm. Immediately after delivery it was noted that on the face, torso and extremities were multiple discrete pinpoint-sized to pinhead-sized petechiae which did not fade on pressure. There were none in the mucous membrane of the mouth. The infant did not appear acutely ill. He was afebrile. The Moro reflex and the tonic reflex of the neck were normal. His eyes were open to observation. There were no paralysis, convulsions or frank hemorrhage from the nose, mouth, umbilicus or anus. The cry was spontaneous and normal. The

1. Sanford, H. M.; Leslie, E. I., and Crane, M. M.: Congenital Thrombocytopenia, Am. J. Dis. Child. **51**:1114 (May) 1936.

2. Davidson, L. T.: Congenital Thrombopenia, Am. J. Dis. Child. **54**:1324 (Dec.) 1937.

3. Whitney, L. H., and Barritt, A. S., Jr.: Spontaneous and Hereditary Thrombopenic Purpura in a Mother and Two Sons, Am. J. Dis. Child. **64**:705 (Oct.) 1942.

4. Urbanski, A. X., and Hutner, C. I.: Thrombopenic Purpura Complicating Pregnancy, J. A. M. A. **120**:754 (Nov. 7) 1942.

5. Schefrin, A. E., and Schechtman, A.: Congenital Thrombopenia, Am. J. Dis. Child. **70**:29 (July) 1945.

6. Morrison, M., and Samwick, A. A.: Congenital Essential Thrombopenic Purpura, Am. J. Dis. Child. **70**:115 (Aug.) 1945.

heart was not enlarged to percussion. There were no cardiac murmurs. Respiration was regular and not labored. The liver and spleen were not palpable. In the right popliteal space was one large purpuric area. The head measured 34 cm., the chest 28.5 cm. and the length 47 cm.

A blood count made at this time showed a hemoglobin concentration of 8.1 Gm. The red cell count was 3,200,000 and the white cell count 12,000, with 92 per cent polymorphonuclear leukocytes and 8 per cent lymphocytes. The color index was 84 per cent. The bleeding time was one and one-half minutes and the coagulation time four and one-quarter minutes. There was no mention made of an unusual number of normoblasts. The platelet count was 63,000 per cubic millimeter. The blood was Rh positive.

Because of the infant's good condition no transfusion was thought necessary. Two milligrams of vitamin K was given prophylactically at once, 1 mg. in six hours and 1 mg. daily for three days. He continued to do well. There was no

Manifestations and Reactions Observed in the Patient and in His Mother and Twin Sister

Criteria * for Thrombopenic Purpura *	Mother	Sister	Patient
1. Purpura with petechiae and ecchymosis	—	—	+
2. Increase in bleeding time	Not done	—	—
4. Decrease in platelets	+	+	+
5. No change in coagulation time	Not done	+	+
10. Normal or slightly enlarged spleen	+	+	+
11. Absence of adenopathy	+	+	+
12. Leukemoid reaction with leukocytosis and polynucleosis	+	+	+
13. Absence of lymphocytosis	+	+	+
14. Absence of leukopenia	+	+	+
Rh factor	+	—	+

* No observations were made with respect to the criteria which have been omitted.

further shower of petechiae, and those present gradually cleared by the time of discharge on the tenth day. Two days later the platelet count rose to 122,000 per cubic millimeter.

The mother of the twins was not permitted to go into labor because of toxemia. With the patient under spinal anesthesia, at term, the cervix was manually dilated. R. M., the first born, was delivered by forceps. J. M., the fraternal twin, was delivered by version and forceps extraction.

R. M. cried spontaneously and presented no signs of abnormality. In view of the fact that her fraternal twin brother had purpura, she too was subjected to laboratory examination. The blood count showed a hemoglobin content of 15.4 Gm. The red cell count was 4,800,000 and the white cell count 17,000, with 74 per cent polymorphonuclear leukocytes, 12 per cent lymphocytes, 12 per cent staff cells and 2 per cent monocytes. The bleeding time was one and one-half minutes and the coagulation time three minutes. There was no mention made of an unusual number of normoblasts. The platelet count was 158,000 per cubic millimeter. The blood was Rh negative.

R. M. was a full term infant weighing 3,091 Gm. Her head was dolichocephalic. The Moro reflex, as well as the tonic reflex of the neck, was normal. The heart was not enlarged to percussion. There were no cardiac murmurs. Respiration was regular and not labored. The liver and spleen were not palpable.

There was no purpura. The fontanelles were not bulging. She was given a prophylactic dose of 2 mg. of vitamin K at once, 1 mg. in six hours and 1 mg. daily for three days. Her neonatal period was uneventful.

COMMENT

Not all the criteria set forth by Morrison and Samwich were fulfilled, but sufficient data were accumulated to substantiate the diagnosis. In view of the fact that both mother and son were Rh positive, erythroblastosis or hemolytic disease of the newborn was ruled out. The absence of abnormal temperature and the good prognosis proved contrary to the diagnosis of toxoplasmosis. The Wassermann reaction of the mother was negative. No determinations for vitamin C were made but, since the purpura regressed without the administration of vitamin C, the presence of scurvy was ruled out on clinical grounds. There was no increase in bleeding time, but Rosenthal showed that the bleeding time may be within normal limits in thrombopenia. Minot stated that a platelet count below 60,000 is conducive to purpura. J. M.'s platelet count was 63,000. Although a determination of prothrombin time was not done, hemorrhagic disease of the newborn was ruled out on clinical grounds. In hemorrhagic disease of the newborn the first manifestations are usually noted on the third or fourth day of life, but may appear as early as the second, and rarely if ever on the first. J. M. was observed to have petechiae almost immediately after birth.

SUMMARY

A case of congenital essential thrombopenic purpura in one of fraternal twins is reported.

The mother and twin sister of the patient had low platelet counts without clinical manifestations of purpura. The platelet count did not reach the critical level of 60,000, which is conducive to the production of purpura.

189 Valentine Lane.

PERNICIOUS ANEMIA IN CHILDHOOD

II. Response to Folic Acid

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NASHVILLE, TENN.

IN A RECENT article[1] a colleague and I reviewed the literature relating to pernicious anemia in childhood and reported the first authenticated case[1a] from America. In this postscript I wish to show the responses of the patient to folic acid.

The patient, A. A., has been followed continuously since November 1940. Throughout she has shown gastric achlorhydria and can be maintained in a state of health only when she is continuously treated for anemia with liver extract or an equivalent. She has been observed through five relapses, some specifically induced by withdrawal of treatment. Erythropoiesis has shown consistently with each relapse an arrest of maturation at the megaloblastic level. She responds in a characteristic way to the administration of liver extract (chart 1).

On Feb. 6, 1946, she received her last injection of liver extract[2] but continued until March 25, 1946, to receive orally 4 cc. of liver extract[3] three times a day. All liver therapy, including food sources, was discontinued on this date, but iron therapy, 0.013 Gm. of ferrous sulfate three times a day, was continued. After the withdrawal of liver therapy she gradually became anemic, and as in previous relapses she began to have diarrhea (five to six stools daily) and to be irritable. The course of her developing anemia is shown in chart 2.

She was readmitted to the hospital on June 26, 1946. Aside from the increased irritability and mild diarrhea she had no symptoms or complaints. Examination revealed her to be pale, sallow and fussy and to have a temperature of 102 F. There were no other significant physical observations. The laboratory data were as follows: The urine was normal. There were 2,400,000[4] and 1,200,000 red blood cells, 5 Gm. of hemoglobin per hundred cubic centimeters and 10,250 white blood cells with 2.5 per cent lymphocytes and 2.5 per cent miscellaneous and unclassified cells. Occasional nucleated red blood cells were seen. There were 190,320 platelets. The color index was 1.39 and the packed cell volume was 21. The gastric analysis showed an absence of free hydrochloric acid after administration of histamine. A stool culture showed Shigella paradysenteriae.

From the Department of Pediatrics, Vanderbilt University School of Medicine.

1. Peterson, J. C., and Dunn, S. C.: Pernicious Anemia in Childhood, Am. J. Dis. Child. **71**:252-268 (March) 1946.

1a. While this paper was in press a prior report of pernicious anemia in a child was called to my attention: Benjamin, B.: Addisonian Pernicious Anemia in Infancy, Am. J. Dis. Child. **50**:1336 (Nov.) 1935.

2. Reticulogen 0.5 cc., equivalent to 10 U.S.P. units; supplied by Eli Lilly and Company.

3. Valentine's oral liver extract, 12 cc., equivalent to 26 U.S.P. units.

4. This count must be in error, as subsequent control counts, of which there were several, were all at the level of 1,200,000 red blood cells.

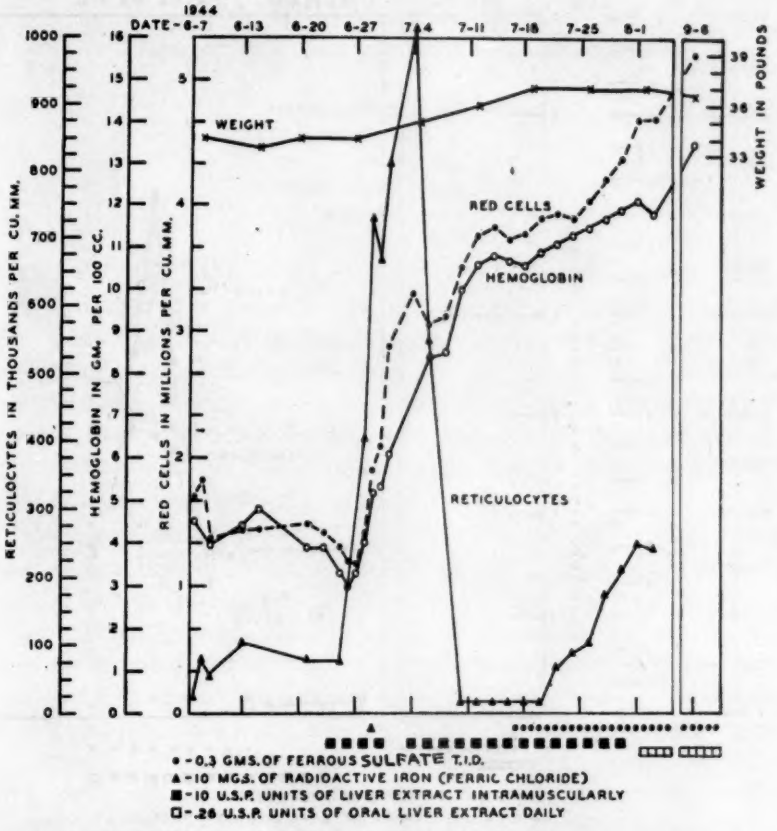

Chart 1.—Changes in the blood and body weight of the patient before and after liver therapy during the fourth admission.[1]

On June 28 oral administration of 5 mg. of folic acid [5] twice a day was started. The response to this treatment is shown in chart 2.

Chart 1 shows the response during her fourth admission to massive doses of liver extract given parenterally. This chart is given for comparison.

After the initiation of treatment with foilc acid the patient became much happier; her fever abated spontaneously, and she ceased to have diarrhea.

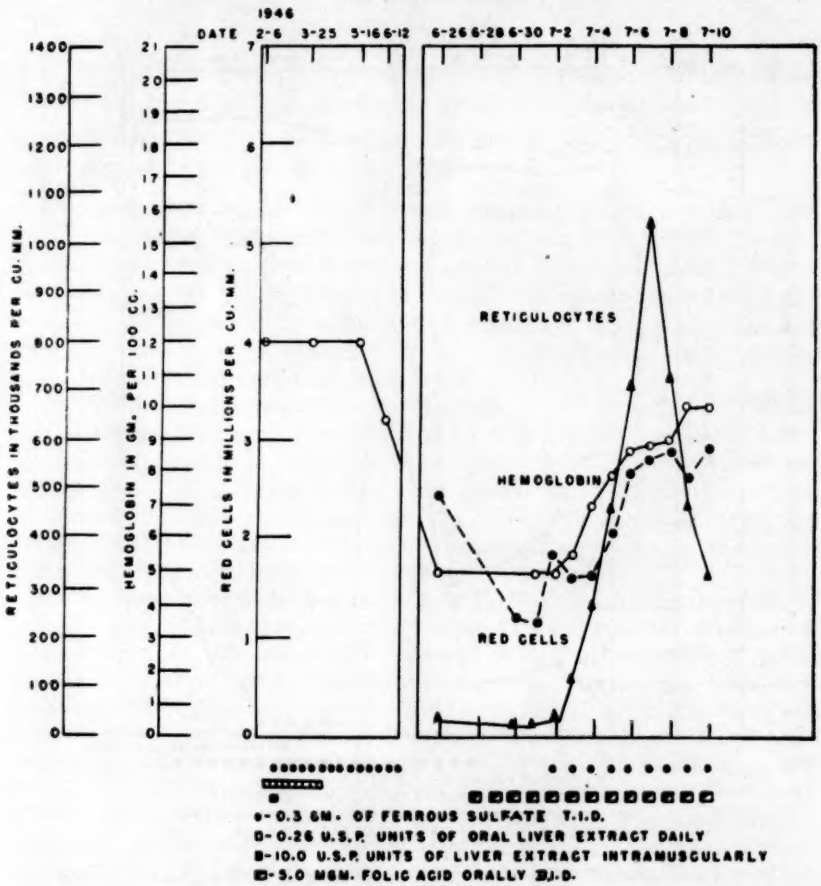
1946
DATE 2-6 3-25 5-16 6-12 6-26 6-28 6-30 7-2 7-4 7-6 7-8 7-10
RETICULOCYTES IN THOUSANDS PER CU. MM.
HEMOGLOBIN IN GM. PER 100 CC.
RED CELLS IN MILLIONS PER CU. MM.
RETICULOCYTES
HEMOGLOBIN
RED CELLS
●- 0.3 GM. OF FERROUS SULFATE T.I.D.
□- 0.26 U.S.P. UNITS OF ORAL LIVER EXTRACT DAILY
■- 10.0 U.S.P. UNITS OF LIVER EXTRACT INTRAMUSCULARLY
▣- 5.0 MGM. FOLIC ACID ORALLY B.I.D.

Chart 2.—Changes in the blood of the patient following the withdrawal of treatment with liver extract and following the administration of folic acid, 10 mg. by mouth daily.

It is apparent from chart 2 that maximal reticulocytosis developed after the administration of folic acid. Administration of folic acid will be continued in the hope that this antianemic substance will maintain the patient in a state of health.

SUMMARY

In a child with pernicious anemia maximal reticulocytosis developed after the oral administration of 10 mg. of folic acid daily.

5. Folic acid used in these studies was purified synthetic material supplied by Lederle Laboratories, Inc.

Progress in Pediatrics

HYPERTENSION IN CHILDREN CAUSED BY PHEOCHROMOCYTOMA

Report of Three Cases and Review of the Literature

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AND
EDWARD HOGE VICK, M.D.
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HYPERTENSION of long duration and serious degree is seldom encountered in pediatric practice, but when it does occur it may offer a most fascinating problem in differential diagnosis. Most cases are due to renal disease, others to coarctation of the aorta, acrodynia, lead poisoning, Cushing's syndrome, hyperthyroidism and rare types of brain tumor involving the hypothalamus. A few cases, by elimination, have to be labeled "essential hypertension," but only after thorough study has failed to reveal the cause.

For most cases of hypertension there is no effective therapy. But there is one further group, illustrated by the 3 cases to be reported here, in which surgical intervention may effect the immediate cure of an otherwise progressive and fatal hypertension. These are the cases due to pheochromocytoma or paraganglioma—tumors of chromaffin tissue which secrete epinephrine. Such tumors usually arise from the adrenal medulla (where they are called "pheochromocytoma"), but occasionally develop from nests of chromaffin tissue (paraganglia) in other parts of the body (in which case they are usually called "paraganglioma"). Histologically these are nearly always benign, and yet they may secrete so much epinephrine into the blood stream as to produce death from hypertensive cardiovascular disease. The clinical picture exhibited by these patients has been called the adrenal-sympathetic syndrome and is characterized most classically by paroxysms of hypertension. A great many, however, show only a steady progressive elevation of the blood pressure.

Three such cases have been seen on the pediatric services of the Presbyterian Hospital and the Long Island College Hospital in New York in the last three years. They are reported because of their rarity and because of their importance from the point of view of the therapy of hypertensive disease.

REPORT OF CASES

CASE 1 (Long Island College Hospital, Brooklyn, N. Y.; service of Dr. Charles Weymuller).—R. R., an exceedingly intelligent and responsive white boy of 11, was admitted to the Long Island College Hospital on Sept. 23, 1943 because of severe headaches of two months' duration. This was complicated, just three days before admission, by pronounced disturbance of his vision. He could no longer read newsprint and complained that near objects would jump from right to left.

While he had always been considered highstrung, he was a well adjusted and popular boy who excelled in school. He had had no infection or other illness which seemed to bear on the syndrome observed at admission.

The year and a half before admission to the hospital was punctuated by mild frontal headaches and aching behind the eyes when he read an ordinary amount. Refraction relieved this complaint until about two months before admission, when the headaches became frequent and severe. They were migratory, sometimes frontal, sometimes occipital, unilateral to either side, but more often bilateral.

Fig. 1 (case 1).—The patient three and five years (on the right and on the left, respectively) before admission, showing the pronounced change in facial expression.

He had these paroxysms of headache almost every day, and on some occasions they would persist throughout the day. They were so severe during the two and one-half weeks before admission that this stoic child cried bitterly with the pain.

During all this time, he had failed little in general health. He had grown 4 inches (10.2 cm.) during the two years before admission but had gained only 2 pounds (907 Gm.) in that time. Except for increased fatigability and mild depression during the severe headaches, he had changed but little.

His appearance was rather striking. He had a tense, exceedingly anxious expression, the look of a person much older than his 11 years, of one who might be suffering from hyperthyroidism. His eyes were somewhat prominent and his subcutaneous tissues rather wasted. His photograph (fig. 1) three years before admission contrasted with one five years before demonstrates the anxious expression and prominent eyes.

At 11 years he was 53 inches (135 cm.) tall and weighed 50 pounds (22.5 Kg.). His abdomen was protuberant, and a blush of his forearms and hands was noted. This blush was not unlike erythredema. His temperature was 99 F. (37.2 C.), and, while his pulse was 120, his blood pressure registered in the vicinity of 260 systolic and 210 diastolic in all four extremities.

Eye studies disclosed slow reaction to stimulation by direct light and to convergence accommodation. There was no extraocular muscular imbalance. The eyegrounds were extensively altered. There was pronounced swelling of each nerve head with associated venous stasis and occasional hemorrhages and large areas of both fresh and old exudate. The arteries showed a slightly widened light streak. Quantitative studies of the visual fields showed a much enlarged blindspot of each eye with extension to the superior periphery of the left field. There was likewise, in each field, a large central scotoma.

His heart beat was extremely rapid and the muscle sounds were sharp, but no cardiac abnormality was evident.

The distended abdomen, so conspicuous in this wasted child, disclosed no tumor mass. His hands and feet were cold, and the aforementioned pink-bronze blush on the extremities was striking. His reflexes were not altered, but were active.

The routine laboratory studies disclosed good hemic component, normal white blood cell count and differential count, no albuminuria or glycosuria, rare hyaline casts on three occasions and negative tuberculin and Wassermann reactions.

Chemical studies of the blood showed no nitrogenous retention: nonprotein nitrogen was 34.2 mg. and uric acid 3.2 mg. per hundred cubic centimeters. The Van Slyke test for urea clearance showed 26.3 per cent of average excretion in the first hour and 76.9 per cent the second hour. The creatinine level was 1.8 mg., the sugar 125 mg. and the cholesterol 217 mg. per hundred cubic centimeters. There was no alteration in the basic elements of the blood. The total base was 156 milliequivalents per liter; the sodium was 144 milliequivalents per liter and the potassium 16 mg. per hundred cubic centimeters. The glucose tolerance was: fasting, 116 mg. per hundred cubic centimeters; then 132 in thirty minutes, 119 in one hour and 106 in two hours.

The basal metabolic rate was estimated at minus 1 and plus 9.

A study of his circulatory system revealed that his heart was slightly enlarged, left ventricular in type, with slight elongation of the aorta. The electrocardiogram showed a P-R interval of 0.16 second, a rate of 105 and the right axis deviation, but no evidence of an intrinsic lesion.

Roentgenologic studies of skull, long bones, abdomen and urinary tract were made. Except for a change in contour of the upper pole of the right kidney, which was disclosed by the intravenous pyelogram, they revealed no abnormality.

The patient's blood produced no effect on cat intestine.

While these data were being collected, the hypertensive level was never less than 200 systolic and there was often a blood pressure of 260 systolic and 220 diastolic. Repeated bouts of severe headache and profuse sweating had no relation to the peaks of blood pressure. Any restriction of his large voluntary intake of fluid was followed by a rise in temperature, a rise in blood pressure and great discomfort.

Just as studies by perirenal injection of air were about to be undertaken, a most dramatic episode occurred. An acute almost manic reaction took place, with disorientation, wild shrieking and violent motions made in apparent extreme pain. His pupils were widely dilated, and the fundi showed 4 D. of disk elevation, further hemorrhages, exudates, arteriovenous nicking and constricted arterioles. The blood pressure was not audible but was easily palpable with the cuff at 300

mm. of mercury. The patient's response to sedation, especially to 10 cc. of 10 per cent magnesium sulfate administered intravenously, was spectacular. The blood pressure fell to 270 systolic and 230 diastolic in ten minuutes, then to 220 systolic and 180 diastolic in fifteen minutes. He became quiet and oriented, and seemed the same as before the episode. Thereafter he maintained a blood pressure of approximately 250 systolic and 210 diastolic, which was not affected by magnesium sulfate given orally or by beta-methylcholine chloride.

Two days later perirenal injection of air (fig. 2) revealed a constant shadow in the region of the right adrenal gland, suggestive of a tumor mass.

Operative removal of the tumor was undertaken. The approach was through a right lumbar incision, with open drop ether as the anesthetic agent. The tumor proved to be the size of a golf ball and was attached to the right adrenal gland.

The reaction of the patient to the operation was catastrophic. Just before operation his blood pressure was 230 systolic and 180 diastolic; under anesthesia

Fig. 2 (case 1).—Perirenal aerogram, revealing a mass in the region of the right adrenal gland.

and just before removal of the tumor it was 220 systolic and 170 diastolic; on ligation it was unobtainable, but it rose to 130 on completion of the operation. There was some response to supportive treatment with adrenal cortex extract, intravenous administration of epinephrine and infusions of isotonic solution of sodium chloride, for the systolic pressure rose again to 180 and the pulse leveled at 94 and respirations at 20.

Two and one-half hours after the operation blood pressure became unobtainable and respirations suddenly ceased, despite the continuous stimulative measures being carried out.

The tumor (fig. 3) proved to be a flattened oval mass of firm tissue covered by a fibrous capsule and measuring 5 by 4 by 2.5 cm. The mass was attached to a bit of adrenal gland measuring 2 by 1 by 1 cm., and extending from this around the circumference of the mass was a narrow rim of adrenal cortex measuring approximately 1 mm. in width. The cut surface of the tumor was made up of

almost uniform, rather soft, bright pinkish yellow tissue in which a few dilated venules and blood sinuses could be seen. There was no necrosis or hemorrhage. Dichromate solution stained the specimen a deep reddish brown, demonstrating beautifully the chromaffinity of the tissue.

Microscopically (fig. 4) the tumor was made up of large epithelial cells arranged in poorly formed acini and in small solid columns. The cytoplasm was abundant and acidophilic. The nuclei were round or oval and contained a moderate amount of diffusely distributed chromaffin granules. In only a few areas was there any noteworthy degree of anaplasia. Delicate vascular strands of fibrous tissue ramified around and between the groups of tumor cells.

This case, the fourth reported in which the patient was below the age of 13, is of interest and importance for several reasons.

The process was definitely existent a year and a half before clinical recognition, and possibly as long as three years. While we can only speculate on the latter period, using the contrasting photographs of the boy at ages 6 and 8 years, one fact stands out clearly. With

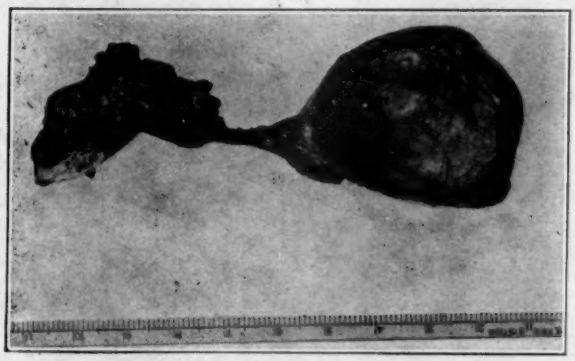

Fig. 3 (case 1).—Pheochromocytoma removed at operation.

earlier diagnosis, before his condition had become physiologically so malignant, the prognosis would have been much more favorable.

His blood pressure, while consistently recorded at extremely high levels, was during the one severe paroxysm the highest recorded in this disease, with diastolic pressure of over 300 mm. of mercury. The dramatic response to administration of magnesium sulfate is noteworthy, although this measure should certainly be used with caution.

Perirenal air studies in this case, as in numerous previous ones, proved of value in localization of the tumor mass.

CASE 2 (Presbyterian Hospital, New York: services of Dr. Rustin McIntosh and Dr. George F. Cahill).—J. L., a white girl aged 12, was first brought to the Presbyterian Hospital on Sept. 2, 1943, complaining of excessive perspiration and failure to gain weight for two years. More recently there had been actual loss of weight, despite an abnormally good appetite. Along with the excessive perspiration there were polydipsia and a pronounced intolerance of hot weather. She had noticed some palpitation, but there was never headache or any true

paroxysms of palpitation, headache or sweating. She was referred by her family physician, who had tested her basal metabolic rate and found it to be plus 50.

The patient was studied in the hospital intermittently for a year, being admitted four times before the correct diagnosis was made. The observations during these admissions may be summarized as follows:

Physically she was of normal height and development for her age, but thin. Her height was 56 inches (142 cm.) and her weight 61 pounds (27.5 Kg.). She seemed tense and anxious, but was quiet and uncomplaining. Her skin was usually warm and moist, though at times she exhibited profuse diaphoresis, with

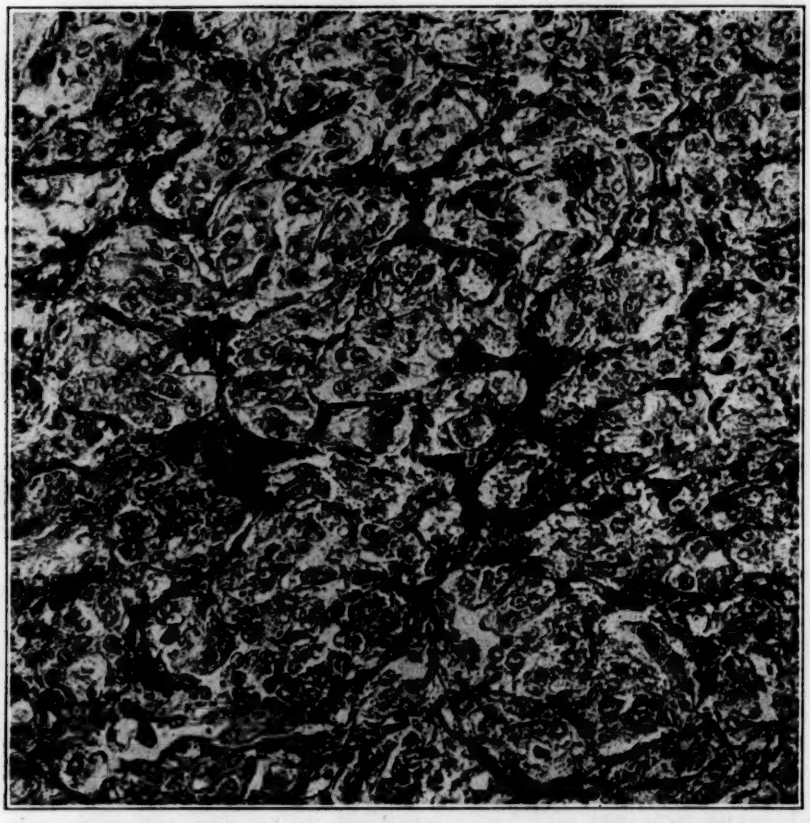

Fig. 4 (case 1).—Photomicrograph of tumor shown in figure 3.

cold extremities. She seemed to suffer unusually from the heat of summer, whereas she was always comfortable with only one blanket in winter. Her pulse ranged between 100 and 110, and the blood pressure was continuously elevated in all four extremities. On the first admission it was 180 systolic and 120 diastolic. Later it rose as high as 240 systolic and 170 diastolic, but never exhibited any unusual lability. The eyegrounds, at first normal, showed progressive development of papilledema (1 to 2 D. bilaterally), arterial spasm and venous compression, hemorrhages and exudates. At the same time visual acuity, at first 20/20 in both eyes, diminished steadily. The pupils were not dilated, and there

was no exophthalmos or lid lag. The lungs were clear to percussion and auscultation. The heart sounds were forceful, with accentuation of the aortic second sound, but no murmurs or cardiac enlargement were detected. Liver, spleen and kidneys could not be felt. No abnormal masses could be felt in the abdomen, and massage of the flanks failed to affect the blood pressure. Extremities and genitalia were normal. There was no suggestion of hirsutism or precocious sexual development. Neurologic examination, including examination of visual fields, revealed no abnormality.

The basal metabolic rate on various occasions was plus 51, 55, 67, 52 and 47. The fasting level of blood sugar was 97 mg. per hundred cubic centimeters. One hour after the ingestion of glucose it was 191, two hours after ingestion 108, three hours after ingestion 69 and four hours after ingestion 60.

All other laboratory findings were normal. Blood counts were all normal. Urinalyses showed specific gravities as high as 1.024, only a trace of albumin, no sugar and no cells or casts in the sediment. The nonprotein nitrogen of the blood was 40 mg. per hundred cubic centimeters. The serum cholesterol level was 213 mg. per hundred cubic centimeters. Kline and Mantoux reactions were negative.

Roentgenologic examination revealed a normal skull, normal heart and lung shadows, a normal intravenous pyelogram, but a tiny fleck of calcium density above the shadow of the left kidney.

Despite the normal iodine level in the blood of 4.8 micrograms per hundred cubic centimeters and lack of any clinical evidence of thyroid disease beyond the elevated metabolic rate, the patient was given a course of treatment with potassium iodide. This had no significant effect on her symptoms, metabolic rate or blood pressure, and seemed effectively to rule out thyrotoxicosis.

On account of the papilledema, tumor of the brain was seriously considered and an electroencephalogram was made. This was normal, and it was planned to attempt ventriculograms, but on account of the fleck of calcium density in the roentgenograms of the abdomen it was decided first to perform perirenal injections of air.

Dr. George Cahill performed the injections, and was able to outline a distinctly enlarged adrenal gland on the left. Accordingly the patient was transferred to the pediatric urology service, under his care, with a diagnosis of pheochromocytoma of the left adrenal gland.

She was operated on by Dr. Cahill on August 17, 1944. Open drop ether anesthesia was used, and the adrenal gland was approached through a left lumbar incision. The gland was found to contain a well encapsulated tumor, which was shelled out without sacrificing the gland itself. Manipulation of the tumor caused a moderate rise in systolic pressure from 170 to 200. On removal of the tumor the pressure fell to 130, but was brought back to the previous level with intravenous administration of epinephrine supplemented with epinephrine in oil and adrenal cortex extract. There was no shock, and the patient left the table in good condition.

The patient's postoperative course was without incident, but surprisingly her symptoms and hypertension failed to abate. She was sent home for a rest and then returned on October 4 for reevaluation. At this time her general condition was about the same as it had been before operation. The blood pressure was 192 systolic and 168 diastolic, and the basal metabolic rate was plus 35. The retinas showed progressive changes with the appearance of star-shaped macular exudates. By this time the vision of her right eye had fallen to 20/70 and of her

left to 20/40. It was evident that unless the hypertension could be soon controlled she was in danger of losing her sight.

It seemed likely that the hypertension now remaining after removal of the tumor might be due to irreversible vascular changes in the kidneys, but there was still the hope that another tumor might be found and removed. In an attempt to ascertain the presence of excessive circulating epinephrine, the patient's freshly drawn blood was twice injected into atropinized cats, but no pressor effect was noted. In fact the first injection caused rapid death of the animal, and the second was followed by a progressive and fatal diminution of blood pressure.

Next a test of adrenolytic drugs was made. The patient was given injections of dimethyl-2, 4-piperidinomethylbenzodioxane (1164 F) and dimethylaminomethyl-benzodioxane (1071 F), two of the benzodioxane drugs first synthesized by Fourneau and shown to have the property of counteracting the effects of epinephrine. These injections produced a rapid fall of 50 mm. of mercury in both the systolic and the diastolic pressure, the effect persisting four minutes. This, we felt, indicated that the hypertension was still due to epinephrine in the blood.

For this reason, and because at the first operation Dr. Cahill had caught a glimpse of what might be a second tumor mesial to the first, he operated again on October 19. This time a transperitoneal approach was used. In the retroperitoneal space, mesial to the left adrenal gland, the second tumor was found. It was about 4 cm. in diameter, and very vascular. All vessels were tied off with the greatest care to avoid manipulation of the tumor. When the tumor was removed, the blood pressure fell to 110 systolic and 85 diastolic, but shock was prevented by the liberal use of epinephrine and adrenal cortex extract.

Again the patient made a good recovery from operation, and this time the symptoms and hypertension gradually disappeared. She was discharged October 30 with a blood pressure of 150 systolic and 115 diastolic and a basal metabolic rate of plus 15.

Since then she has been followed in the clinic. A note dated November 15 says, "Blood pressure is 124 systolic and 80 diastolic. There is no more perspiration, palpitation, heat intolerance, polyphagia or polydipsia. She has gained 5 pounds (2.3 Kg.) since discharge." On December 20 the blood pressure was 116 systolic and 60 diastolic. It has been normal ever since. When last seen, on April 4, 1946, the patient was in vigorous health, having gained 28 pounds (12.7 Kg.) and a healthy respect for cold weather since discharge. Her blood pressure was 116 systolic and 80 diastolic, her basal metabolic rate plus 5 and her visual acuity 20/20 in boths eyes, with complete disappearance of papilledema, hemorrhages and exudates.

Pathologic Data.—The tumor removed from the left adrenal gland was examined by Dr. Dorothy H. Andersen. According to her report it weighed 6 Gm. and measured 2.3 by 2.4 by 1.5 cm. The cut surface was yellowish buff and marked into irregular lobules. A few deep yellow flecks were visible grossly. After standing overnight in 10 per cent formaldehyde the tumor became gray, while the solution of formaldehyde was stained a clear bright yellow. This solution was studied by Dr. De Witt Stetten Jr., who found that the color disappeared with addition of hydrochloric acid, to reappear on neutralization with potassium hydroxide. The color turned a deep green with ferric chloride, suggesting the presence of epinephrine or some closely related compound.

Microscopically the tumor consisted of rounded masses of cells separated by a thin fibrous stroma. Each mass contained 15 to 50 cells and occupied one quarter to one half of a high power field. The cells had large pale nuclei with

fine, distinct granules and also fine threads of chromatin. Sometimes there was one nucleolus, often none. Mitoses were occasionally found, but the cells showed no inclination to pass the barrier of the fibrous capsule. The Wiesel and Schmorl stains demonstrated clearly many chromaffin granules in the cytoplasm. The pathologic diagnosis was pheochromocytoma of the adrenal gland.

The second, extramedullary, tumor was examined by Dr. Meyer M. Melicow. Its cut surface presented the same mottled yellowish brown appearance seen in the first tumor. Microscopically it resembled that tumor in all essentials, and with Schmorl's stain showed large quantities of chromaffin material.

An acid aqueous extract of the extramedullary tumor was tested qualitatively for epinephrine by one of us (C. H. S.). The extract was dropped into the conjunctival sacs of a rabbit which had previously undergone a unilateral cervical sympathectomy. The pupil of the denervated eye dilated maximally, while the extract had no effect on the normal eye. The only known substance which behaves in this way is epinephrine.

Tissue cultures from the tumor were made to grow successfully by Dr. Margaret Murray, but attempts to identify epinephrine in the culture medium were unsuccessful. No quantitative assays for epinephrine were attempted.

This is the fifth recorded case of pheochromocytoma with hypertension in the pediatric age group, and the second such case in which cure was effected by operation. It is the first case at any age that has presented two tumors, one being intramedullary and the other extramedullary. It indicates the importance of considering pheochromocytoma in the differential diagnosis of hypertension in children, even when the hypertension is continuous rather than paroxysmal.

CASE 3 (Grasslands Hospital, Valhalla, N. Y., service of Dr. Duncan Barnes, and Presbyterian Hospital, New York, service of Dr. George F. Cahill).—D. B., a colored girl aged 11, was first seen at Grasslands Hospital, where the diagnosis of pheochromocytoma was made. She was later transferred to the Presbyterian Hospital for treatment. Dr. Duncan Barnes of Grasslands Hospital permitted us to publish the data obtained during her stay there.

The onset of her illness appears to date from 1942, when she began to have attacks of headache, sometimes accompanied by vomiting and abdominal distress. According to the mother the patient used to be sent home from school on account of attacks of abdominal pain. On arriving home she would appear extremely nervous and covered with perspiration. During this period she was seen at various clinics, where no abnormality was ever found, and her blood pressure was said to be normal. She was never examined during one of her attacks, and by the time she was seen by us the paroxysmal nature of her illness had disappeared.

In the autumn of 1945 she was brought to her family physician because of dyspnea on exertion. He found pronounced cardiac enlargement and referred her to the Grasslands Hospital, where she was admitted on December 19. The observations made there and later at the Presbyterian Hospital are summarized in the following paragraphs:

The patient was a tall, thin Negro girl, rather apprehensive and unusually disturbed by any painful procedure such as venipuncture. Her extremities were usually cold and her skin moist, the face and trunk being frequently drenched with perspiration, especially after any excitement. Her height was 60 inches (153 cm.) and her weight 77 pounds (35 Kg.). The temperature was normal, the

pulse 90 to 130. The blood pressure varied between 180 systolic and 136 diastolic and 230 systolic and 145 diastolic, with a pulsus alternans of 10 to 20 mm. Later, when she was digitalized, her blood pressure rose to 270 systolic and 175 diastolic. The pupils were equal and not dilated. Fundiscopic examination showed pronounced narrowing and tortuosity of the arteries, nicking of the veins and a beginning star-shaped macular exudate, but no papilledema. The thyroid was not palpable. The lungs were clear. The heart was enlarged, the apex beat being 10 cm. to the left of the midsternal line in the fifth interspace. Heart sounds were forceful, with a few extra systoles and a soft apical systolic murmur. Examination of the abdomen revealed no abnormality; no mass could be felt, and massage of the flanks did not raise her blood pressure. Extremities and genitalia were normal; there was no hirsutism or evidence of precocious genital development. Neurologic examination, including studies of the visual fields, showed no abnormality.

Blood counts were all normal. The urine concentrated to 1.024, contained little albumin (0 to plus 1), no sugar and no cells or casts in the sediment. The blood sugar was 102 mg. per hundred cubic centimeters during fasting, 133 a half hour after ingestion of glucose, 67 at one and one-half hours and 91 at two and one-half hours after ingestion. The nonprotein nitrogen was 33 mg. per hundred cubic centimeters. Excretion of phenolsulfonphthalein was normal. The serum cholesterol was 229 mg. per hundred cubic centimeters. The serum sodium was 131 milliequivalents per liter and the potassium 4.5 milliequivalents per liter.

Roentgenograms of skull and abdomen were normal. The roentgenogram of the chest showed a large globular heart shadow, interpreted as enlargement particularly of the left ventricle. The electrocardiogram was normal except for tachycardia and left axis deviation.

The basal metabolic rate on three occasions was plus 67, 48 and 53. The iodine in the blood was not measured, but the patient was given an oral dose of radioactive iodine, after which 12 per cent of the dose appeared in the thyroid area in twenty-four hours, indicative of normal thyroid activity.

Because the clinical picture suggested hyperadrenalinemia, this patient was also tested with adrenolytic drugs. She received intravenous injections of dimethyl-2, 4-piperidinomethylbenzodioxane (1164 F) and piperidinomethylbenzodioxane (933 F) and responded with a dramatic drop in both systolic and diastolic pressures of 50 mm. of mercury lasting ten minutes. This seemed to confirm the diagnosis of pheochromocytoma, but the question of localizing the tumor remained. Perirenal insufflation of air was carried out by Dr. Cahill, but both adrenal glands appeared normal and no evidence of tumor could be found.

Nevertheless, on account of the convincing clinical evidence of hyperadrenalinemia and the results of the benzodioxane tests, and also because it was evident that her heart was failing and that the patient could not survive long without intervention, an exploratory laparotomy was performed by Dr. Cahill on Feb. 21, 1946. Anesthesia was with solution of tribromoethanol and ether, and the abdomen was opened through a transverse incision in the upper part of the abdomen. Two masses were found. One, the size of a cherry, lay on the right near the bifurcation of the aorta. The other, as big as an orange, lay retroperitoneally on the right, filling the foramen of Winslow. It was independent of both kidney and adrenal gland but intimately attached to the vena cava, the aorta and the duodenum, being overlain by the common bile duct and the portal vein. The small mass was removed easily, but the slightest handling of the larger mass caused a sharp rise of the blood pressure followed by an alarming drop. Only a beginning could be

made of the difficult task of freeing the mass from the duodenum when, despite the greatest care the blood pressure, which had oscillated widely, fell to zero and the heart stopped in systole. Efforts to revive the patient with intravenous administration of ergotamine tartrate and piperidinomethylbenzodioxane were of no avail. Portions of the tumor were removed for study, but permission for complete autopsy was refused.

Pathologic Data.—Both tumors presented a yellowish buff lobulated appearance on section. The microscopic appearance was the same in both—namely, clusters of polyhedral cells separated by highly vascular connective tissue trabeculae. The cells had large round or oval hyperchromatic vesicular nuclei, and in the cytoplasm abundant granules of chromaffin material were seen with Schmorl's stain. Pathologic diagnosis was paraganglioma (pheochromocytoma) of (*a*) the right adrenal region and (*b*) the region of the aortic bifurcation (organ of Zuckerkandl?). Identification of epinephrine in the tumors was not attempted.

This case, the sixth case of pheochromocytoma with hypertension in a child, probably represents an example of paroxysmal hypertension that went on to become continuous. Such a sequence of events has been commonly noted among adults with the disease, since it was first observed by Vaquez, Donzelot and Geraudel. Had the original attacks been recognized for hypertensive episodes, it is possible that the diagnosis could have been made at a time when the tumor was operable. Hence the importance of such procedures as the histamine test (Roth and Kvale), by which paroxysms of hypertension may be induced at will for the benefit of the examining physician.

Another important lesson to be drawn from this case and the preceding one is that the diagnosis of pheochromocytoma can be made with assurance even without roentgenologic evidence of a tumor, in which case laparotomy will almost invariably reveal its location. Nevertheless, in retrospect it seems possible that, although pyelograms and perirenal aerograms were normal, the tumor might have been localized by roentgen visualization of the duodenum, as was done by Volhard.

It is interesting to speculate on the cause of death in these all too common cases in which the patients dies on the table apparently from the circulatory effects of manipulation of the tumor. In this case blood was drawn from the heart at the time of death and contained 13 milliequivalents per liter of potassium in the serum, said to be a lethal concentration. It has been reported by Fenn that the intravenous injection of epinephrine in human beings produces a rise in the serum potassium. MacKeith and Strickler have found the serum potassium to be elevated in their patients with pheochromocytoma.

REVIEW OF THE LITERATURE

MacKeith in a recent review found 165 cases of pheochromocytoma reported in the literature up to 1944. Many of these, however, were incidental findings at autopsy, with no history of hypertension. After

a careful search of the literature through 1945 we have found only 84 cases of proved pheochromocytoma in which there is convincing evidence of hyperadrenalinemia. Of these 45 are established beyond question because their hypertension was cured by removal of the tumor. In the other 39, although successful operation was not performed, there can be no doubt of the diagnosis because they had not only proved pheochromocytoma but they exhibited the typical adrenal-sympathetic syndrome.

There remains a group of 31 cases in which there was proved pheochromocytoma plus hypertension. The majority of these probably represent true hyperadrenalinemia, but there is not enough evidence in the reports to rule out the possibility of nonfunctioning pheochromocytoma with an incidental coexisting essential hypertension. For the sake of accuracy these cases will be omitted from the following discussion, as also will 4 cases in which the only evidence for hypertension is the autopsy findings of cardiac enlargement and arteriosclerosis, the pressure not having been measured during life, and an additional 6 cases of sudden unexplained death attributed by the pathologist to pheochromocytomas found at autopsy.

The following analysis, then, is based on the 84 proved cases, including our own 3 cases.

Age at the Time of Diagnosis.—Pheochromocytoma has rarely been diagnosed in childhood. Of all the verified cases of pheochromocytoma with hypertension in the literature, prior to this, only 3 have occurred in children under 13.[1] In addition there were 9 cases in which the patients were in their teens. In the third decade of life there have been 19 cases, in the fourth decade 22, in the fifth 17, in the sixth 6 and in the seventh 2. The oldest patient was 69.

Since we are particularly interested in the pediatric age group, it may be of interest to review the 3 cases reported in children prior to this publication.

CASE 1 (Evans).—The patient was a white girl aged 12. She had suffered for four years with typical paroxysms of palpitation and headache, excessive sweating and polyphagia. During attacks her blood pressure went as high as 285 systolic and 230 diastolic. The eyegrounds showed papilledema, arterial spasm and exudates. Her basal metabolic rate was plus 60. Before she could be operated on she died in an attack, and at autopsy a tumor the size of a hen's egg was found behind the tail of the pancreas and attached to the left adrenal gland. This was histologically a pheochromocytoma.

1. A fourth case in a boy of 10 was recently reported by Espersen and Dahl-Iversen. The patient had persistent hypertension due to pheochromocytoma which was not demonstrated by exploratory operation. The patient died six hours after operation. Necropsy revealed a malignant pheochromocytoma in front of the large vessels. It was connected by a small pedicle with the lower mesial angle of the left adrenal gland.

CASE 2. (Linneweh).—The patient was a white boy aged 10 who had been sick for a year, with a diagnosis of chronic nephritis. His symptoms were progressive weakness and loss of weight, visual disturbances, "cold sweats," polydipsia and polyuria. He never had anything suggestive of a hypertensive paroxysm. On examination he was emaciated and had a sustained blood pressure of 215 systolic and 165 diastolic. The eyegrounds showed severe albuminuric retinitis. The urine was normal except for slight albuminuria. Blood urea was normal, and the fasting level of blood sugar was 114 mg. per hundred cubic centimeters. Pyelograms showed a normal renal pelvis and ureter on the right but pronounced hydronephrosis and hydroureter on the left. The diagnosis of hypertension due to unilateral renal disease was made, and nephrectomy done on the left. This failed to cure the hypertension, but at operation a tumor of the left adrenal gland was seen, and was removed at a later operation. This also failed to cure the patient, who by this time was having convulsions accompanied by loss of consciousness and profuse diaphoresis. Six weeks after the second operation the boy died in congestive heart failure, and at necropsy a second tumor was found in the right adrenal gland. Both these tumors were chromaffin, and as the right kidney appeared normal the author plausibly attributes the hypertension to the bilateral pheochromocytomas.

CASE 3 (Neff, Tice, Walker and Ockerblad).—This case is even more extraordinary than the last. It concerns a girl who showed hirsutism at the age of 8 months and acne at 11 months, and when seen at 16 months showed obesity, generalized hirsutism particularly involving the pubic region, a bone age of over 2 years and large adult-like genitalia. The systolic pressure ranged from 140 to 180 mm. of mercury. The red cell count was 6,380,000, the hemoglobin 76 per cent, the urine normal, and the nonprotein nitrogen, the blood sugar and the glucose tolerance normal. Pyelograms and perirenal aerograms showed a mass above the left kidney. There was a delay of a month before operation, during which time the blood pressure rose gradually to 200 systolic and 110 diastolic, and the tumor became palpable. There were never any paroxysms of hypertension. At operation manipulation of the tumor caused a rise in blood pressure, and on clamping off its blood supply the tension fell to 80. The child left the table in good condition, however, and follow-up after a year showed a normal healthy infant with a normal blood pressure and complete regression of the hirsutism and genital changes. The tumor was 6 cm. in diameter, weighed 96 Gm. and histologically was strictly a medullary tumor of the adrenal gland with abundant chromaffin granules and no trace of adrenal cortical elements. The authors were at a loss to explain the growth of hair and genitalia, which of course is not part of the adrenal-sympathetic syndrome. They suggest a functional derangement of the adrenal cortex through the mechanical pressure of the underlying medullary tumor.

For the sake of completeness we should mention the case of von Neusser and Wiesel, who reported finding at autopsy in a 2 year old infant a chromaffin tumor of the adrenal medulla associated with microscopic evidence of advanced arteriosclerosis. Presumably this infant had hypertension, but the clinical data are not given.

The 9 cases reported in patients between 13 and 20 years of age need not be reviewed in detail, since their disease differed in no way from that seen in adults. Five of them were operated on, with 2 deaths and 3 cures. The case of the 18 year old girl reported by Frankel in 1886 makes interesting reading because it is the first description

of the syndrome of paroxysmal hypertension, and although written at a time before the sphygmomanometer was in use the description of the clinical picture is so vivid as to leave no doubt as to the diagnosis.

Clinical Features.—The one sine qua non for the clinical diagnosis of pheochromocytoma is hypertension. This may be paroxysmal or not. In the 84 proved cases in the literature it was paroxysmal in 52 and constant in 15, and in 14 there were paroxysms with an elevated blood pressure during the intervals as well. However, if we were to include the 31 cases in which the hypertension was probably due to the tumor but not proved to be so, the proportion of cases with sustained hypertension would be much higher. It is interesting that of the 6 children in the group, only 1 (that of Evans) showed the classical paroxysmal picture.

The typical hypertensive paroxysm has been described many times since the classical descriptions of Fränkel and of Labbé, Tinel and Doumer, but no one has improved on these authors. The patient is ordinarily entirely well except during attacks, and these may come only once a month or as often as several times in a day. Attacks are ushered in by a feeling of weakness and apprehension, sometimes a fulness or "rising" in the epigastrium. Then come palpitation and headache, progressing to a pounding in the chest and throbbing in the head so severe as to prostrate the patient completely. The skin becomes pale, the hands cold and the expression anxious, and the pupils may dilate. At this time the blood pressure may reach levels over 300 mm. of mercury systolic, while the diastolic usually, though not invariably, rises proportionately. The attack lasts a few minutes to many hours, and as it passes the skin flushes and the patient breaks out with a profuse diaphoresis.

In less classical but perhaps not less numerous cases the patients have no paroxysms but are apt to present almost continually the palpitation, headache, anxiety, cold extremities and especially the hyperhidrosis that are seen in the typical attacks. Besides these symptoms there are no physical findings that are at all specific for the disease. Hypertensive retinopathy and cardiac enlargement are common in this and all other forms of hypertensive disease. Abdominal palpation is usually negative; in only 10 cases has the tumor been palpable on physical examination.

Most important of all, one must remember that all the enumerated signs and symptoms may be absent with the exception of hypertension. Such cases will invariably be diagnosed as essential hypertension unless the clinician is unusually alert to the possibility of finding a tumor and thus giving the otherwise doomed patient an opportunity for radical cure by surgical intervention. A case in point is that of Thorn, Hindle and Sandmeyer. A 40 year old woman with sustained hyper-

tension for seven years and no symptoms except headache was being studied preparatory to treatment by sympathectomy. The intravenous pyelogram showed the left kidney to be displaced downward. She was operated on and a pheochromocytoma removed; her blood pressure has been normal ever since.

Laboratory Data.—Glycosuria is reported in 14 of the 80 cases, hyperglycemia in 17 and abnormally high glucose tolerance in 8. Cases with paroxysmal hypertension of course may show these changes only during paroxysms.

The basal metabolic rate has been elevated in 14 cases, the highest figure being plus 74. Commonly it is plus 40 to plus 60. But in 12 cases it has been normal. The apparent discrepancy seems inexplicable at present. Patients with paroxysmal hypertension might be expected to show a normal metabolic rate during the intervals when the blood pressure is normal, but 5 patients showed a normal rate even at times when their blood pressure was elevated.

Otherwise the ordinary laboratory tests are of no help in diagnosing this condition. It is interesting. however, that in 3 cases a high serum potassium level has been noted.

Special Diagnostic Procedures.—When the diagnosis of pheochromocytoma is suspected, various procedures may be employed in an effort to bring on an attack of hypertension. The commonest is to massage the region of the adrenal glands. Other methods that have succeeded in various cases are hyperventilation, exposure to heat, the cold pressor test and injections or insulin or histamine. Some patients have themselves learned how to bring on an attack, as by bending to one side or backward, or by distending the stomach with food or fluid. A test based on the ability of histamine to provoke an attack has recently been standardized by Roth and Kvale (1945). We have had no experience with it, but it is certainly significant when the reaction is positive.

In cases without paroxysms, such as ours, the mentioned tests will be of no value. In these the ideal test would be one that would assay the amount of epinephrine in the blood. This was first accomplished by Beer, King and Prinzmetal, who perfused the patient's plasma through the isolated rabbit's ear and demonstrated a potent vasoconstrictor effect reversible by ergotamine. Hyman and Mencher, using the dog's tail and the denervated cat's eye as indicators, demonstrated epinephrine in blood taken from their patient during a paroxysm. We had no success in our patients with relatively crude tests on cat's intestine and the cat's blood pressure.

Several chemical methods for the identification of epinephrine have been tried on the blood of these patients. Most of them depend on the decolorization of methylene blue and are not generally considered

reliable or specific. With such methods Strömbeck and Hedberg found that the level of epinephrine in their patient's blood was thirty times normal between attacks and a thousand times normal during attacks. Volhard found only a slight excess of epinephrine in his patient's blood during attacks, while Biskind, Meyer and Beadner and Mortell and Whittle were unable to demonstrate any hyperadrenalinemia in their patients by chemical methods.

On the whole, chemical methods are unreliable and biologic ones are cumbersome, and there is at present no practical clinical method for assaying epinephrine in the blood. That is why in our last 2 cases we resorted to the use of adrenolytic drugs for diagnosis. The test with benzodioxane drugs (Goldenberg, Snyder and Aranow) proved valuable in them.

Localization of the Tumor.—The tumor was palpable on physical examination in only 10 of the 84 reported cases. In some others it could be localized because massage on one side induced a paroxysm. Otherwise one must resort to the use of roentgen rays, including pyelography and perirenal insufflation of air. In a few cases simultaneous visualization of duodenum and renal pelves, as recommended by Volhard, may help. More recently De Vries and his colleagues recommended tomography.

Chromaffin tumors have been found in many parts of the body. Anatomically chromaffin tissue is located not only in the adrenal medulla but also in connection with all of the sympathetic ganglions and the carotid body and organ of Zuckerkandl, so that in theory a pheochromocytoma or paraganglioma could develop in any of the sites. The fact remains that all of the 84 verified cases of hypertension caused by pheochromocytoma have shown tumors in or close beside the adrenal gland. Two cases have been reported with the tumor in the mediastinum and 1 with the only tumor at the bifurcation of the aorta (organ of Zuckerkandl), but these are among the cases in which the hypertension was not certainly caused by the tumor. Our third case, of course, presented two tumors of which the smaller appeared to arise from the organ of Zuckerkandl. Because these extramedullary tumors may escape detection by any roentgenologic method, patients with the adrenal-sympathetic syndrome should be explored whether or not the site of the tumor is known.

Finally, the possibility of multiple tumors must not be ignored. In 5 of the 80 reported cases there have been multiple tumors, but in none have there been more than two. Our second case illustrates that the failure of surgical extirpation to cure the disease may be due to the presence of a second functioning tumor.

Treatment.—The only treatment is surgical extirpation. To date 58 patients have been operated on, with 45 cures and 13 deaths, a

mortality of 22 per cent. This represents a high risk, but without operation death eventually supervenes. The mortality will perhaps be reduced a bit by preoperative preparation, more careful anesthesia and surgical technic and the proper use of pressor or adrenolytic drugs during operation, but the only way to lower it materially is by early diagnosis.

Nonsurgical methods of therapy are of theoretic interest. Roentgenologic treatment was used by Vaquez and seemed to stop the attacks of hypertension, but they returned after a year and the patient eventually died of the disease. Rogers found "slight improvement" after roentgen therapy. It seems reasonable that roentgen rays might be used in preparation for operation, to minimize the danger of overloading the circulation with epinephrine when the tumor is handled.

Of the adrenolytic drugs, ergotamine has been most employed. Labbé, Hegglin and Nabholz and Engel used it intramuscularly and intravenously with no success. Biskind and his colleagues gave it to their patient over a period of several months, during which it appeared to relieve the headaches. Later it seemed to have no effect on either the headaches or the hypertension. Hyman and Mencher gave their patient 0.75 cc. of ergotamine tartrate intramuscularly, after which the blood pressure fell in a minute from 190 to 130, but in another patient Mencher found that 1 cc. of the drug given intravenously had no effect on the hypertension.

Intravenous administration of calcium seemed to stop the attacks in the patient of Kalk and Buchner, but no subsequent reports of its use have been found. In our first case intravenous administration of magnesium sulfate proved invaluable in controlling a severe hypertensive episode.

The benzodioxane drugs were first employed by Labbé, who gave his patient a hypodermic injection of diethylaminomethylbenzodioxane (883 F), which failed to reduce the hypertension. We have used these drugs for diagnosis but feel that they have no place in therapy because of the unpleasant side effects.

SUMMARY

Three cases of hypertension due to pheochromocytoma in children are reported. These are the fourth, fifth and sixth such cases in the literature. In all 3 there was a severe continuous hypertension rather than the classical paroxysmal hypertension. They thus illustrate the importance of considering pheochromocytoma in the differential diagnosis of any long-standing hypertension.

All 3 patients were operated on; 1 was cured, while 2 died. The one success shows what a gratifying result may sometimes be attained

when a severe and disabling hypertensive disease is radically cured by operation.

The literature of pheochromocytoma has been reviewed. Altogether only 84 proved cases of hypertension due to pheochromocytoma are reported to date. Of these only 3, prior to this report, have occurred in children. These 3 cases are described briefly.

The clinical features, laboratory data, diagnosis and treatment of the disease have been reviewed.

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BIBLIOGRAPHY

(References are given below in chronological order for all of the eighty-one proved cases of hypertension due to pheochromocytoma reported prior to this publication.)

Fränkel, F.: Ein Fall von doppelseitigem, völlig latent verlaufen Nebennierentumor und gleichzeitiger Nephritis mit Veränderungen am Circulationsapparat und Retinitis, Virchows Arch. f. path. Anat. **103**:244-263, 1886.

von Neusser, E., and Wiesel, J.: Die Erkrankungen der Nebennieren, in Nothnagel, C. W. H.: Spezielle Pathologie und Therapie, ed. 2, Vienna, W. Hölder, 1910, p. 158.

Labbé, M.; Tinel, J., and Doumer: Crises solaires et hypertension paroxystique en rapport avec une tumeur surrénale, Bull. et mém. Soc. méd. d. hôp. de Paris **46**:982-990, 1922.

Masson, P., and Martin, J. F.: Paragangliome surrénale, Bull. Assoc. franç. p. l'étude du cancer **12**:135-143, 1923.

Mayo, C. H.: Paroxysmal Hypertension with Tumor of Retroperitoneal Nerve, J.A.M.A. **89**:1047-1050 (Sept. 24) 1927.

Labbé, M.; Azérad, E., and Violle, P. L.: Adénome médullaire surrénal et hypertension paroxystique, Bull. et mém. Soc. méd. d. hôp. de Paris **53**:952-956 (July 8) 1929.

Shipley, A. M.: Paroxysmal Hypertension Associated with Tumor of Suprarenal, Ann. Surg. **90**:742-749 (Oct.) 1929.

Vaquez, H.; Donzelot, E., and Géraudel, E.: Le surrénalome hypertensif, Presse méd. **37**:169-173 (Feb. 6) 1929.

Peyron, A.: Le paragangliome surrénale et son syndrome cardiovasculaire, Bull. Assoc. franç. p. l'étude du cancer **19**:618-650 (July) 1930.

Porter, M. F., and Porter, M. F., Jr.: Report of Case of Paroxysmal Hypertension Cured by Removal of Adrenal Tumor, Surg., Gynec. & Obst. **50**:160-162 (Jan.) 1930.

Lazarus, J. A., and Eisenberg, A. A.: Tumors of Adrenal Gland, J. Urol. **27**: 1-26 (Jan.) 1932.

Rogers, E.: Paroxysmal Hypertension Associated with Ganglioneuroma of Suprarenal Medulla, Am. Heart J. **8**:269-274 (Dec.) 1932.

Bauer, J., and Leriche, R.: Contribution clinique et thérapeutique à l'étude des paragangliomes et des crises d'hypertension adrénalinique, Presse méd. **42**: 1385-1388 (Sept. 5) 1934.

Belt, A. E., and Powell, T. O.: Clinical Manifestations of Chromaffin Cell Tumors, Surg., Gynec. & Obst. **59**:9-24 (July) 1934.

Coller, F. A.; Field, H., Jr., and Durant, T. M.: Chromaffin Cell Tumor Causing Paroxysmal Hypertension, Relieved by Operation, Arch. Surg. **28**:1136-1148 (June) 1934.

Ernould, H., and Picard, F.: Un cas de sympathome symathogonique avec hypertension artérielle paroxystique, Rev. belge sc. méd. **6**:223-251 (March) 1934.

Kalk, H.: Paroxysmale Hypertension, Klin. Wchnschr. **13**:613-617 (April 28) 1934.

Labbé, M., and Nepveux, F.: Un cas d'hypertension paroxystique, Bull. et mém. Soc. méd. d. hôp. de Paris **50**:337-347 (March 5) 1934.

Suermondt, W. F.: Paroxysmale Blutdruckerhöhung geheilt durch Extirpation einer Nebennierengeschwulst, Zentralbl. f. Chir. **61**:70-74 (Jan. 13) 1934.

van Goidsenhoven, F., and Appelmans, R.: Contribution à l'étude clinique et thérapeutique de l'hypertension paroxystique d'origine médullo-surrénalienne, Bull. Acad. roy. de méd. de Belgique **14**:672-694 (Nov.) 1934.

Burgess, A. M.; Waterman, C. W., and Cutts, F. B.: Adrenal Sympathetic Syndrome with Unusual Variations in Cardiac Rhythm: Report of Case, Arch. Int. Med. **58**:433-447 (Sept.) 1936.

Gärtner, W.: Das klinische Bild, insbesondere die Kreislaufstörungen, bei Paragangliom der Nebenniere, Ztschr. f. Kreislaufforsch. **28**:82-90 (Feb. 1) 1936.

Kelly, H. M.; Piper, M. C.; Wilder, R. M., and Walters, W: Case of Paroxysmal Hypertension with Paraganglioma of Right Suprarenal Gland, Proc. Staff Meet., Mayo Clin. **11**:65-70 (Jan. 29) 1936.

Kremer, D. N.: Medullary Tumor of Adrenal Glands, with Hypertension and Juvenile Arteriosclerosis, Arch. Int. Med. **57**:999-1007 (May) 1936.

Landau, A.; Paszkiewicz, L.; Slawinski, Z., and Steffen, E., Jr.: Hypertension paroxystique grave consécutive à une tumeur de la surrénalienne, Rev. belge sc. méd. **8**:330-343 (May) 1936.

Beer, E.; King, F. H., and Prinzmetal, M.: Pheochromocytoma with Demonstration of Pressor (Adrenaline) Substance in Blood Preoperatively During Hypertensive Crisis, Ann. Surg. **106**:85-91 (July) 1937.

Edward, D. G. F.: Pheochromocytomata and Hypertension with Details of a Case, J. Path. & Bact. **45**:391-403 (Sept.) 1937.

Evans, V. L.: Suprarenal Tumor with Paroxysmal Hypertension, J. Lab. & Clin. Med. **22**:1117-1120 (Aug.) 1937.

Howard, J. E., and Barker, W. H.: Paroxysmal Hypertension and Other Clinical Manifestations Associated with Benign Chromaffin Cell Tumors (Pheochromocytomata), Bull. Johns Hopkins Hosp. **61**:371-410 (Dec.) 1937.

Wells, A. H., and Boman, P. G.: Clinical and Pathologic Identity of Pheochromocytoma, J.A.M.A. **109**:1176-1180 (Oct. 9) 1937.

Binger, M. W., and Craig, W. M.: Atypical Case of Hypertension with Tumor of Adrenal Gland, Proc. Staff Meet., Mayo Clin. **13**:17-20 (Jan. 12) 1938.

Borras, P. E., and Meyer Mota, M.: Paraganglioma de la suprarenal, Semana méd. **1**:990-994 (May 5) 1938.

Brenner, F.; Konzett, H., and Nagl, F.: Ueber ein Phäochromocytom der Nebenniere, München. med. Wchnschr. **85**:914-916 (June 17) 1938.

Brunschwig, A.; Humphreys, E., and Roome, N. W.: Relief of Paroxysmal Hypertension by Excision of Pheochromocytoma, Surgery **4**:361-370 (Sept.) 1938.

Hegglin, R., and Nabholz, H.: Das Nebennierenmarksyndrom: Zur Kasuistik der chromaffinen Geschwülste; Mit einem Beitrag über den Adrenalinnachweis von H. Fischer, Ztschr. f. klin. Med. **134**:161-195, 1938.

Holst, E. J.: Three Cases of Chromaffin Cell Tumors of Suprarenal Glands, Acta med. Scandinav. **94**:510-526, 1938.

MacKenzie, D. W., and McEachern, D.: Tumor of Medulla of Adrenal (Adrenal Pheochromocytoma) with Removal and Relief of Paroxysmal Hypertension, J. Urol. **40**:467-476 (Oct.) 1938.

Palmer, R. S., and Castleman, B.: Paraganglioma of Adrenal Gland Simulating Malignant Hypertension, New England J. Med. **219**:793-796 (Nov. 17) 1938.

Bensis, W., and Codounis, A.: Contribution à l'étude de l'hypertension paroxystique du médullosurrénalome, Bull. Acad. de méd., Paris **121**:237-256 (Feb. 21) 1939.

Strömbeck, J. P., and Hedberg, T. P.: Tumor of Suprarenal Medulla Associated with Paroxysmal Hypertension, Acta chir. Scandinav. **82**:177-189, 1939.

Allen, P. L.: Chromaffin Cell Tumor with Paroxysmal Hypertension, Texas State J. Med. **36**:540-542 (Dec.) 1940.

Baumgarten, E. C., and Cantor, M. O.: Pheochromocytoma: Case Report, Ann. Surg. **111**:112-116 (Jan.) 1940.

Brunschwig, A., and Humphreys, E.: Excision of Pheochromocytoma Following Near Fatal Attack of Paroxysmal Hypertension, J.A.M.A. **115**:355-357 (Aug. 3) 1940.

Hamilton, J. E.: Pheochromocytoma of Adrenal with Paroxysmal Hypertension: Case Relieved by Surgery, Kentucky M. J. **38**:572-575 (Dec.) 1940.

Hatieganu, I.; Moga, A., and Radu, P.: Ueber Veränderungen des Blutbildes (Lymphocytose) während der Hochdruckkrisen bei hypertensiven Suprarenalom (Paragangliom), Zentralbl. f. inn. Med. **61**:337-344 (May 25) 1940.

Fenn, W. O.: Role of Potassium in Physiological Processes, Physiol. Rev. **20**: 377-415 (July) 1940.

Van Epps, E. F.; Hyndman, O. R., and Greene, J. A.: Clinical Manifestations of Paroxysmal Hypertension Associated with Pheochromocytoma of Adrenal, Arch. Int. Med. **65**:1123-1129 (June) 1940.

Biskind, G. R.; Meyer, M. A., and Beadner, S. A.: Adrenal Medullary Tumor: Pheochromocytoma Cured by Surgical Intervention; Clinical Management; Analysis of All Reported Operated Cases, J. Clin. Endocrinol. **1**:113-123 (Feb.) 1941.

Crana, J. J.; Alesen, L. A., and Touriel, E. L.: Tumor of Suprarenal Medulla Associated with Paroxysmal Hypertension: Report of Case Preoperatively Diagnosed and Cured by Surgical Removal, J. Urol. **46**:1100-1102 (Dec.) 1941.

Heath, F. K.; Cahill, G. F., and Atchley, D. W.: Pheochromocytoma: Correct Diagnosis and Successful Operation, J. A. M. A. **117**:1258-1260 (Oct. 11) 1941.

Nettleship, A.: Adrenal Medullary Tumor, J. Clin. Endocrinol. **1**:124-125 (Feb.) 1941.

Rømske, O.: Paroxysmal Hypertension Due to Adrenal Pheochromocytoma: Case, Nord. med. **12**:2953-2955 (Oct. 18) 1941.

Engel, F. L.; Mencher, W. H., and Engel, G. L.: Epinephrin Shock as Manifestation of Pheochromocytoma of Adrenal Medulla: Report of Case with Successful Removal of Tumor, Am. J. M. Sc. **204**:649-661 (Nov.) 1942.

Evans, W. F., and Stewart, H. J.: Peripheral Blood Flow in Case of Pheochromocytoma Before and After Operation, Am. Heart J. **24**:835-842 (Dec.) 1942.

Linneweh, F.: Ueber eine seltene Form des blassen Hochdrucks, Monatschr. f. Kinderh. **90**:179-192, 1942.

McCullagh, E. P., and Engel, W. J.: Pheochromocytoma with Hypermetabolism: Report of Two Cases, Ann. Surg. **116**:61-75 (July) 1942.

Neff, F. C.; Tice, G. M.; Walker, G. A., and Ockerblad, N.: Adrenal Tumor in Female Infant with Hypertrichosis, Hypertension, Overdevelopment of External Genitalia, Obesity, but Absence of Breast Enlargement, J. Clin. Endocrinol. **2**:125-127 (Feb.) 1942.

Strickler, C. W., Jr.: Pheochromocytoma: Operative Failure; Case Report, South. Surgeon **11**:193-199 (March) 1942.

Hyman, A., and Mencher, W. H.: Pheochromocytoma of Adrenal Gland, J. Urol. **49**:755-776 (June) 1943.

Lecuire, J.; Galy, P., and Galy: Médullo-surrénalome avec hypertension paroxystique: Diagnostiqué, opéré et guéri, Presse méd. **51**:443 (Aug.) 1943.

Duncan, L. E., Jr.; Semans, J. H., and Howard, J. E.: Adrenal Medullary Tumor (Pheochromocytoma) and Diabetes Mellitus: Disappearance of Diabetes After Removal of Tumor, Ann. Int. Med. **20**:815-821 (May) 1944.

Mencher, W. H.: Paroxysmal Hypertension Caused by Pheochromocytoma: Adrenalectomy, J. Mt. Sinai Hosp. **10**:743-746 (Jan.-Feb.) 1944.

Kvale, W. F.; Roth, G. M.; Clagett, O. T., and Dockerty, M. B.: Headache and Paroxysmal Hypertension: Observations Before and After Surgical Removal of Pheochromocytoma, S. Clin. North America **24**:922-933 (Aug.) 1944.

MacKeith, R.: Adrenal-Sympathetic Syndrome, Brit. Heart J. **6**:1-12 (Jan.) 1944.

Thorn, G. W.; Hindle, J. A., and Sandmeyer, J. A.: Pheochromocytoma of Adrenal Associated with Persistent Hypertension: Case Report, Ann. Int. Med. **21**:122-130 (July) 1944.

Volhard, F.: Ein Fall von paroxysmalen Hochdruck infolge Nebennierenmarktumor, durch Operation geheilt, München. med. Wchnschr. **91**:120 (March 10) 1944.

Mortell, E. J., and Whittle, J. P.: Pheochromocytoma: Case Report with Certain Observations on Pathologic Physiology, J. Clin. Endocrinol. **5**:396-402 (Nov.) 1945.

Padis, N.: Paroxysmal Hypertension Caused by Adrenal Tumors: Report of Three Cases, Clinics **4**:87 (June) 1945.

Roth, G. M., and Kvale, W. F.: A Tentative Test for Pheochromocytoma, Am. J. M. Sc. **210**:653-660 (Nov.) 1945.

De Vries, A.; Mandl, F.; Rachmilevitz, M., and Ungar, H.: Paroxysmal Hypertension Due to Adrenal Medullary Tumor, Surgery **19**:522 (April) 1946.

Espersen, T., and Dahl-Iversen, E.: Clinical Picture and Treatment of Pheochromocytomas of Adrenals, Acta chir. Scandinav. **94**:271 (July) 1946.

Goldenberg, M.; Snyder, C. H., and Aranow, H., Jr.: A New Test for Hypertension Due to Circulating Adrenalin, read before the New York Academy of Medicine Jan. 21, 1947.

Abstracts from Current Literature

Biochemistry; Bacteriology, and Pathology

THE EFFECT OF TRIETHYLENE GLYCOL VAPOR ON AIR-BORNE BETA HEMOLYTIC STREPTOCOCCI IN HOSPITAL WARDS. MORTON HAMBURGER JR., VALERIE HURST, O. H. ROBERTSON and THEODORE T. PUCK, J. Infect. Dis. **77**:177 (Nov.-Dec.) 1945.

The bactericidal effect of triethylene glycol vapor on air-borne hemolytic streptococci in hospital wards at relative humidities of 18 to 32 per cent was found to be substantial, though the reductions were less than those achieved when the humidity was maintained at 40 to 50 per cent. The effect was noted both on streptococci liberated into the air during bed making and on those present during "quiet periods."

The implications of this effect for the practical application of glycol vapors are discussed.

TOOMEY, Cleveland.

IN VITRO SUSCEPTIBILITY OF HISTOPLASMA CAPSULATUM TO THERAPEUTIC AGENTS. JOHN H. SEABURY and DOROTHY ARTIS, Proc. Soc. Exper. Biol. & Med. **61**:15 (Jan.) 1946.

Five day old cultures of Histoplasma capsulatum in heart-brain broth were treated with various concentrations of drugs, and the cultures were examined at the end of seven days. Sulfadiazine, sulfathiazole, nitrogen glucoside of sodium paraaminophenylstibonate, streptomycin and penicillin were found to exert no inhibitory effect on the concentrations used. Neoarsphenamine in a concentration of 100 mg. per hundred cubic centimeters and 4,4-diamidinostilbene, 10 to 100 mg. per hundred cubic centimeters, prevented the growth of the organisms.

HANSEN, Galveston, Texas.

Metabolism; Infant Feeding; Milk and Other Foods

RESULTS OF PROVIDING A LIBERALLY ADEQUATE DIET TO CHILDREN IN AN INSTITUTION: I. ACCEPTANCE OF FOODS AND CHANGES IN THE ADEQUACY OF DIETS CONSUMED. LYDIA J. ROBERTS, RUTH BLAIR and MARJORIE GREIDER, J. Pediat. **27**:393 (Nov.) 1945.

The diets of children in an institution were supplemented for a year with all foods necessary to provide the amounts advised in the commonly accepted dietary pattern. The supplements included milk and other dairy products, eggs, whole grain cereals and pineapple juice. Daily records were kept of the amounts of each food consumed, and a quantitative dietary study was made at the beginning and close of the year to determine the changes in amounts of various nutrients ingested by the individual children.

The acceptance of all foods was unusually good. In 94 to 99 per cent of times offered all these foods were accepted by the children, usually in amounts equal to or in excess of the dietary pattern.

The original diets were below the recommended dietary allowances for all factors except vitamin A; the factors most deficient were thiamine and vitamin C.

The intakes of nutrients on the improved diet were sufficient to bring them up to and in most cases well above the allowances. The specific contributions made by the different foods are described.

These data being interpreted in connection with the changes in physical status reported in other papers, it is concluded that the supplemented diet supplied some factor or factors which were present in the initial diet in suboptimal amounts. The applications of these observations to the feeding of children in institutions and elsewhere are discussed.

AUTHORS' ABSTRACT.

RESULTS OF PROVIDING A LIBERALLY ADEQUATE DIET TO CHILDREN IN AN INSTITUTION: III. BLOOD AND URINARY EXCRETION STUDIES BEFORE AND AFTER DIETARY IMPROVEMENT. HELEN OLDHAM, LYDIA J. ROBERTS and MARJORIE YOUNG, J. Pediat. **27**:418 (Nov.) 1945.

The levels of vitamin A, carotene, hemoglobin and thiamine in the blood and of proteins in the serum were determined for a group of 39 boarding school children; determinations of vitamin C in the plasma were made for the entire population of the school; fasting, one hour excretions and four hour returns of thiamine and riboflavin test doses were studied for groups of 30 or more children. All determinations were made in the autumn when the children were receiving the institutional diet and were repeated in the spring after the diet had been improved by extensive supplementation which brought the intakes of all nutrients up to or in excess of the recommended allowances.

The only values which were undesirably low in the institutional diet and which were significantly improved in the supplemented diet were those concerned with vitamin C and thiamine. Both the level of vitamin C in the plasma and of thiamine in the blood, which in many children were low in the autumn, showed significant improvement in the spring. The returns of test doses and the one hour fasting excretions of thiamine which were also low in many cases on the institutional diet were higher on the improved diet.

The returns of riboflavin test doses, which were relatively high on the institutional diet, showed no significant change on the supplemented diet. The fasting one hour excretions of riboflavin, however, were considerably higher in the spring than in the autumn.

These results are in complete agreement with those of a dietary study which was made at the same time and which showed the institutional diet to be furthest below the recommended dietary allowances in thiamine and vitamin C. This furnishes further support to the usefulness of biochemical measurements of nutritional status.

Until such time as additional evidence is presented, it is suggested that normal children who have been consuming the type of diet that is generally recommended will have in the majority of cases blood values which are not appreciably lower than 0.6 mg. of vitamin C, 6 micrograms of thiamine and 75 international units of vitamin A per hundred cubic centimeters; that they will return 7 per cent or more of an oral test dose of 75 micrograms of thiamine per kilogram of weight and 20 per cent or more of a similar test dose of riboflavin in four hours, and that the fasting one hour excretions of thiamine and riboflavin will not be significantly less than 6 and 9 micrograms, respectively.

AUTHORS' SUMMARY.

SEVERE AND PROLONGED UNDERFEEDING IN AFRICAN CHILDREN (THE KWASHIORKOR SYNDROME OF MALIGNANT MALNUTRITION). H. C. TROWELL, Arch. Dis. Childhood **20**:110 (Sept.) 1945.

A critical review is offered of a severe syndrome of malnutrition seen in African children and called kwashiorkor. It manifests itself chiefly as failure of growth, edema, macrocytic anemia, steatorrhea, crazy pavement dermatosis, fatty liver and decreased albumin but increased globulin in the plasma and deficiency bowel pattern.

In varying degrees this syndrome affects about three quarters of the sick children in Kampala, Uganda, between the ages of 6 months and 3 years.

A detailed study is offered of the infections detected in 180 cases. Malaria was present in about two thirds, intestinal infections by protozoa and helminths in about one half and congenital syphilis in one tenth.

The syndrome may be refractory to all forms of treatment; a limited trial of desiccated hog's stomach supplementing a diet high in proteins and in calories has given encouraging results and is worthy of a more protracted trial.

KELLY, Milwaukee.

STUDIES OF PHYSICOCHEMICAL REGULATION OF RESPIRATION AND ACID BASE EQUILIBRIUM IN CHILDHOOD. H. BRÜHL, Ann. pædiat. **160**:148 (March) 1943.

The direct determination of the organic acids in blood serum by means of ultrafiltration and electrotitration normally gives an average value of 9.09 millimoles with a spread of 7.5 to 13 millimoles. In rachitis values between 4 and 10 millimoles of organic acids were found. The values were, therefore, definitely decreased. It is pointed out that György and his co-workers obtained low lactic acid values in rachitis serum. The organic acids increase during healing of rachitis. Latent tetany behaves like rachitis, as also do continuous spasms. In eclamptic tetany the organic acids are increased. The simultaneous examination of arterial blood and sinus blood in manifest tetany shows higher values in arterial than in sinus blood. The difference is 2 to 6.25 millimoles. As previously shown, organic acids are consumed in a higher degree in the excitement metabolism of the nervous system.

AUTHOR'S SUMMARY.

EXPERIMENTS ON VITALITY OF HUMAN MILK. G. PICCARDI and P. E. MESSERI, Riv. di clin. pediat. **44**:3, 1946.

This first series of measurements of the superficial tension of human milk and its variations in successive moments after extraction, made with the ring method, have shown that this tension notably increases ten to fifteen minutes after the milk has been pumped out of the breasts. This increase is a sign that, as clinical data have already shown, milk undergoes a certain transformation which probably is not merely of a physical character.

AUTHORS' SUMMARY.

BREAST FEEDING IN COPENHAGEN DURING THE FIRST SIX MONTHS OF LIFE. POVL HERTZ, Ugesk. f. læger **104**:1055 (Oct. 8) 1942.

The author gives data on breast feeding for 25,000 infants during the three year period 1938 to 1941. During the neonatal period 93.3 per cent of the infants born at home were exclusively breast fed, while the corresponding figures for infants born in private obstetric clinics and in a maternity hospital were 81.9 and 80 per cent, respectively. Of the three groups 2.4, 6.3 and 6.6 per cent, respectively, were exclusively bottle fed. An increase in incidence of breast feeding could be shown during the neonatal period for infants born at home (81 per cent in 1933 and 90.1 per cent in 1938), while breast feeding was less frequent during the neonatal period in the maternity hospital (85.2 per cent in 1933 and 78.5 per cent in 1938). At the age of 6 months 13.4 per cent of the children were exclusively breast fed in 1940, and an additional 36.1 per cent got mixed feeding. The author concludes that there is no reason to believe that breast feeding is less frequent now than previously but emphasizes the importance of propaganda and interest for the feeding of the infants in the maternity hospitals.

WALLGREN, Stockholm, Sweden.

Vitamins; Avitaminoses

PHYSIOLOGICAL AVAILABILITY OF THE VITAMINS: V. THE EFFECT OF COPPER ON EXTRA DIETARY ASCORBIC ACID. MELVIN HOCHBERG, DANIEL MELNICK and BERNARD L. OSER, J. Nutrition **30**:225 (Oct.) 1945.

M. Hochberg, D. Melnick and B. L. Oser presented data to show that no destruction of ascorbic acid occurred in the digestive system as the result of the taking of copper along with the vitamin in doses of 200 mg. and 7 mg. respectively. These results were in agreement with the data obtained in the test in vitro.

FREDEEN, Kansas City, Mo.

PHYSIOLOGICAL AVAILABILITY OF THE VITAMINS: VI. THE EFFECT OF ADSORBENTS ON THIAMINE. DANIEL MELNICK, MELVIN HOCHBERG and BERNARD L. OSER, J. Nutrition **30**:233 (Oct.) 1945.

Studies of availability of vitamins in human beings were conducted by D. Melnick, M. Hochberg and Bernard L. Oser to determine the influence of the concomitant ingestion of two adsorbents, impure aluminum silicate (fullers' earth) and kaolin on the availability of thiamine. These materials readily adsorb thiamine from aqueous solution. The availability of the vitamin was considerably reduced by the fullers' earth and not by kaolin, which appeared to protect the vitamin during its passage through the gastrointestinal tract so that a greater than theoretic value for available thiamine was obtained.

FREDEEN, Kansas City, Mo.

EFFECT OF SOYBEAN PHOSPHATIDES ON VITAMIN A METABOLISM. CHARLES A. SLANETZ and ALBERT SCHARF, J. Nutrition **30**:239 (Oct.) 1945.

Charles A. Slanetz and Albert Scharf investigated the storage in the liver and the blood levels of vitamin A in the rat as influenced by specific factors used as supplements in a purified basal diet containing synthetic B vitamins instead of yeast. Commercial soybean lecithin considerably influenced storage and blood levels of vitamin A in the rat. Iodine interfered with this effect, while the heated soybean lecithin interfered little.

FREDEEN, Kansas City, Mo.

FIELD ILLUMINATION AND COMMERCIAL HANDLING AS FACTORS IN DETERMINING THE ASCORBIC ACID CONTENT OF TOMATOES RECEIVED AT THE CANNERY. G. FRED SOMERS, KARL C. HAMNER and WALTER L. NELSON, J. Nutrition **30**:425 (Dec.) 1945.

G. F. Somers and his colleagues found little loss in ascorbic acid in tomatoes during the picking and the transportation of the fruit to the cannery; however, considerable variation was found from one tomato field to another. Data were presented which indicated that the amount of light for eighteen days prior to harvest was closely correlated with the ascorbic acid content of tomatoes under field conditions, which may account for the variations observed in the ascorbic acid content of market tomato juice.

FREDEEN, Kansas City, Mo.

THE EFFECT OF MANUFACTURING METHODS ON THE ASCORBIC ACID CONTENT AND CONSISTENCY CHARACTERISTICS OF TOMATO JUICE. WILLARD B. ROBINSON, ELMER STOTZ and Z. I. KERTESZ, J. Nutrition **30**:435 (Dec.) 1945.

W. B. Robinson and his colleagues showed that under efficient manufacturing conditions tomato juice should contain at least 80 per cent of the ascorbic acid content of the trimmed tomatoes, and this was independent of the preheating temperature. The latter caused only variations in the consistency of the juice. Considerable loss may occur during excessive holding of the hot juice in an open tank, but little during processing in the can.

FREDEEN, Kansas City, Mo.

SECRETION OF VITAMIN D IN MILKS OF WOMEN FED FISH LIVER OIL. LOUIS J. POLSKIN, BENJAMIN KRAMER and ALBERT E. SOBEL, J. Nutrition **30**:451 (Dec.) 1945.

L. J. Polskin, B. Kramer and A. E. Sobel concluded that for the purpose of fortifying human milk with vitamin D for infant use administration of supplementary fish liver oil to the mother during pregnancy was not a practical method. Vitamin D must be taken just prior to or during lactation in order to enrich the milk with the factor appreciably.

FREDEEN, Kansas City, Mo.

So-Called Vitamin-Resistant Rickets. Marlies Lüssy, Ann. pædiat. **166**:11 (Jan.) 1946.

Two cases of rickets resistant to vitamin D are discussed neither of which seems to belong to the usual types (renal, hepatic and enteral) but which present remarkable peculiarities.

The first case is due to a pluriglandular endocrine disturbance with dwarfism. Diagnosis was confirmed by postmortem examination. High stoss doses of vitamins resulted in therapeutic failure. Histologically, the prevalent feature was pronounced osteoporosis in addition to the usual arrest of enchondral and periosteal ossification. In the bone marrow many osteoclasts were found.

In the second case the rickets was only relatively vitamin resistant. The clinical picture was exactly like that described by Albright and his co-workers. Considerable improvement was achieved with massive dosage (900,000 international units daily). Dihydrotachysterol (A. T. 10) as well as vitamin D in much increased dosage had been unsuccessful. The conception that an insufficiency of the parathyroids is responsible seems to be untenable for such cases. The considerable delay in the appearance of the ossification centers in the carpus points to an endogenous factor. This delay was in no way influenced by the large and repeated doses of vitamin D_2. They had only a symptomatic effect, but did not promote a permanent cure of this particular type of rickets. The moment that the treatment was stopped the inorganic phosphate fell to low values. The initial increase of the serum chlorides and the arrest of growth were remarkable.

Author's Summary.

Prematurity and Congenital Deformities

Congenital Malformations of the Extremities with Special Reference to Congenital Clubfoot. R. Scherb, Helvet. pædiat. acta **1**:99 (Nov.) 1945.

The work of W. Brandt on the larvae of amphibians in the cauda-budding stage and the conclusions drawn by him as to the genesis of malformations of the limbs are discussed, as well as his theories on induction and determination.

The hypotheses of various authors as to the origin of congenital clubfoot are mentioned. In previous communications, the author attributed this deformation to the persistence of a phylogenic residue originating in the fetal shaping of the extensor brevis digitorum and interposed between the peroneus brevis and the tuberosity of the fifth metatarsal bone; this residue normally disappears during the third month of embryonic life. The origin of congenital clubfoot could thus be rendered possible by the action of a gene inhibiting the general development and shaping of the entire foot and preventing the phenomena of induction from eliminating the phylogenic residue before the critical or irreversible phase of determination. This residue thus persists and develops with the foot which, during the third month of embryonic life, is deformed and becomes a congenital clubfoot. The existence of a specific isolated clubfoot gene is therefore not likely.

Author's Summary.

Bonnevie-Ullrich Syndrome: Its Clinical Picture According to the Cases at the Children's Hospital of Zurich. Ettore Rossi, Helvet. pædiat. acta **1**:134 (Nov.) 1945.

Fourteen cases presenting the Bonnevie-Ullrich syndrome in which treatment was given at the Children's Hospital in Zurich are described and discussed.

The syndrome consists of a pterygium of the neck, the axilla, the elbows and the hollows of the knees. Besides there are lymphangiectatic edema, hypertelorism with epicanthus, high gothic palate, hypoplasia of the breasts and infantilism. Often the digital impressions of the skull are increased and other stigmas of degeneration are found. The cause and the pathogenesis of the syndrome are

discussed. The author is in favor of the hypothesis of Bonnevie that the malformations are due to a disturbance in the secretion of the spinal fluid, that—because of hereditary factors—an abnormal secretion of spinal fluid exists because the fluid goes through the foramen anterior (Weed) into the subcutaneous tissue and produces edema. The hypothesis could be advanced that by the action of secondary genes the Bonnevie-Ullrich syndrome is produced from a degenerate genotypus.

AUTHOR'S SUMMARY.

Newborn

PENICILLIN LOCALLY IN THE EYES OF NEWBORN INFANTS TO PREVENT OPHTHALMIA NEONATORUM. ALLAN BLOXSOM, J. Pediat. **27**:447 (Nov.) 1945.

In a nursery for newborn infants, after 1 infant had contracted gonorrhea ophthalmia neonatorum penicillin (250 units per cubic centimeter) was used locally every four hours in the eyes of 20 contacts. No new case developed, and it is suggested that penicillin instead of the irritating silver salts should be used in the eyes of the newborn at birth to prevent ophthalmia neonatorum.

AUTHOR'S ABSTRACT.

RIGHT SIDED TRANSIENT PARALYSIS OF THE DIAPHRAGM IN A NEW BORN. J. VICTOR GREENEBAUM and FOREST G. HARPER, J. Pediat. **28**:483 (April) 1946.

The occurrence in the New Born Service at the Jewish Hospital of the first recognized case of isolated injury of the phrenic nerve with paralysis of the diaphragm merits a report since it is the eighth such recorded case. Diaphragmatic paralysis has been recognized since 1902, when Naunyn reported the first case.

The authors' patient was a boy who cried well and breathed normally when delivered after the removal of mucus from his throat. He did well for three days, but then had some difficulty with his breathing. On the seventh day the outstanding signs were cyanosis and rapid labored respirations which were thoracic in type and limited chiefly to the left side. Under the fluoroscope the mediastinum moved to and fro with each respiration as a result of the paradoxic or seesaw movement of the diaphragm. The heart was displaced to the left and downward but the contour was normal. A roentgenogram confirmed the high diaphragm at the level of the fifth rib on the right side.

The infant was placed on the right side for splinting, oxygen was given continuously and gavage feedings were given. When last seen, at the age of 5 months, the infant weighed 15 pounds, 4 ounces (6,917 Gm.), breathed normally and appeared to be in excellent condition.

AUTHORS' ABSTRACT.

PURULENT PLEUROPERICARDITIS AND BRONCHOPNEUMONIA IN A NEWBORN INFANT. JOSE R. MONTALVO, Bol. Soc. cubana de pediat. **17**:488 (Dec.) 1945.

The author presents a case of purulent pleuropericarditis and bronchopneumonia in a newborn infant. In the review of the literature the author found cases of pericarditis, empyema and pneumonia in newborn infants but not the association of the three processes. The mother, 25, multipara, was admitted during the last month of pregnancy with a history of a temperature around 103 F. of three days' duration and was treated with sulfathiazole; in three days the temperature was normal. Nine days after admission spontaneous delivery of a 10 pound (4,536 Gm.) infant occurred. The placenta was fairly normal and the amniotic fluid was clear. On examination the baby showed generalized cyanosis, dyspnea, a temperature of 104 F., a weak cry and diminished cardiac tone. Roentgen examination revealed granular enlargement of the cardiac shadow, fracture of the right clavicle and a bronchopneumonic process of the right apex. Oxygen and sulfadiazine were of no avail, and the infant died the following day. At necropsy purulent fluid was observed in both pleural cavities, and the pleura and the pericardium were thickened

with a small amount of purulent fluid in the pericardial cavity. Histologically, there was a bronchopneumonic process in the upper lobe of the right lung. Pneumococcus type I was found in pleural and pericardial fluid and also in the vaginal discharge of the mother five days after delivery. The author comments that the infection probably took place through the placenta.

KEITH, Rochester, Minn.

LESIONS OF THE SPINAL CORD FROM BIRTH TRAUMA. HANS ZELLWEGER, Helvet. pædiat. acta **1**:13 (Aug.) 1945.

Injuries of the spinal cord caused by birth may be divided into two groups: 1. Lesions in vertex presentation concern almost exclusively the upper part of the cervical cord and are incompatible with extrauterine life. The trauma of the birth itself is less important for these contusions of the spinal cord than certain anomalies of the position and the motility of the vertebral column. 2. Injuries in breech presentation can be found in every part of the spinal cord. The birth trauma itself proves to be of highest importance for the origin of these lesions. In nearly all the cases known to the author as well as in 3 cases of his own there were difficult deliveries. In these cases more than 50 per cent of the infants die at birth or shortly after birth. In 3 cases of the author's and in several in the literature the infants survived the first six months.

AUTHOR'S SUMMARY.

Acute Contagious Diseases

CHANGING TRENDS IN DIPHTHERIA IN SAN FRANCISCO. J. P. GEIGER, Arch. Pediat. **62**:510 (Nov.) 1945.

A brief report is made of experience with diphtheria in San Francisco between 1922 and 1944. The progressively and greatly decreasing incidence of cases is emphasized together with the increasing affection of persons in the age group of 30 years and over. Further, the increasing fatality rate is considered as evidence of increasing virulence of the causative organism.

GRULEE JR., Minneapolis.

SUSCEPTIBILITY OF VERVET MONKEYS TO POLIOMYELITIS VIRUS IN FLIES COLLECTED AT EPIDEMICS. JOSEPH L. MELNICK and ROBERT WARD, J. Infect. Dis. **77**: 249 (Nov.-Dec.) 1945.

Flies trapped in four epidemic areas in 1943 and 1944 were tested for poliomyelitis virus in vervet (Cercopithecus aethiops pygerythrus) monkeys from East Africa. Eleven of this species of monkey were used for these tests. Experimental poliomyelitis was produced in 2 vervet monkeys inoculated with flies from two of these epidemic areas, urban Chicago and rural North Carolina, respectively. This indicates that another experimental host, at present more available than cynomolgus or Java monkeys, is susceptible to poliomyelitis virus in flies.

TOOMEY, Cleveland.

THERAPEUTIC EFFECT OF STREPTOMYCIN IN EXPERIMENTAL MURINE PERTUSSIS. W. L. BRADFORD and ELIZABETH DAY, Proc. Soc. Exper. Biol. & Med. **60**:324 (Dec.) 1945.

Intranasal installations of freshly isolated strains of Hemophilus pertussis in various dilutions were made in groups of standard 3 week old white Swiss mice, after which the mice were kept under uniform environmental conditions. Streptomycin hydrochloride dissolved in distilled water was injected into the mice four hours later and continued every four hours for four to five days. It was found that it required more than ten times the number of organisms to kill the treated than the untreated mice. In another strain the ratio was 3 to 1. Also, there was a

distinct difference in the percentage of surviving mice showing negative cultures of material from the lungs. In other experiments streptomycin was found to have definite protective action, whereas penicillin had none. The authors believe their observations to be sufficiently convincing to justify a trial in the human disease; these studies are already under way.

HANSEN, Galveston, Texas.

SHORT WAVE TREATMENT OF WHOOPING COUGH. STEVAN RECHT, Ann. pædiat. **163**:26 (July) 1944.

A preliminary condition of every therapy is to establish an exact diagnosis as soon as possible and to ascertain the existence of the disease and its stage. Concerning pertussis short wave therapy is to be considered first. In the early stage short wavelengths and little energy are applied; later longer waves and more energy can be used. This therapy is made more effective by the administration of expectorants and sedatives, eventually combined with injections of mother's blood and Paragen (a complex, nonspecific protein preparation containing a quinoline-urea compound). Of 110 patients treated in this way, within twelve days 58 per cent, within sixteen days 85 per cent and within twenty days 95 per cent showed remarkable improvement. In these cases the improvement becomes evident not only by disappearance of the clinical symptoms but also roentgenologically. The best results were obtained when the therapy was given in an early stage of the disease. In a large proportion of the cases this treatment moderates the symptoms most effectively. Complications were not observed.

AUTHOR'S SUMMARY.

TRAUMA AND HEINE-MEDIN DISEASE. CALAMARI, Riv. di clin. pediat. **44**:18, 1946.

The author has studied the problem of the connection between trauma, in the widest sense, and poliomyelitis. After a brief review of the literature, 9 cases in which poliomyelitis had been shortly preceded by direct or indirect trauma of the nervous system are reported. The trauma factor is emphasized as a pathogenic factor in Heine-Medin disease.

The author recommends that every precaution be taken against any kind of trauma during an epidemic of poliomyelitis.

AUTHOR'S ABSTRACT.

PENICILLIN AND CARRIERS OF LOEFFLER'S BACILLUS. R. MAGNOL and M. E. IGLESLAS, Arch. de pediat. d. Uruguay **16**:606 (Oct.) 1945.

The authors found the results of local application of penicillin encouraging in the management of 7 diphtheria carriers. Though the abstracts of individual cases are not entirely clear, it appears that local use of penicillin deserves more careful evaluation.

PLATOU, New Orleans.

ANALYSIS OF TWO YEARS OF DIPHTHERIA AT THE HOSPITAL DEL NIÑO. PEDRO DANIEL MARTÍNEZ, Bol. méd. d. hosp. inf., México **2**:357 (Jan.-Feb.) 1946.

The author analyzed the 112 registered cases of diphtheria at the Hospital del Niño during its first twenty-four months of activity. A corrected mortality rate of 3.5 per cent was found. All the deaths except one were attributed to diphtheritic myocarditis. No patient with laryngeal diphtheria had cardiac complications, and none died after a stay of twenty-four hours at the hospital. Nasal and laryngeal diphtheria were sometimes confused with congenital syphilis and acute laryngitis, respectively. Of 6 patients with diphtheritic paralysis, 5 had myocarditis. A single dose of diphtheria antitoxin was sufficient in every case. Thirty-five per cent of the children that stayed over six days at the hospital had serum sickness. Local application of penicillin was of no effect. A detailed description of the hospital routine is given.

MADERO, México, D. F., Mexico.

BONE MARROW IN WHOOPING COUGH. ROBERT F. LANDOLT, Helvet. pædiat. acta **1**:153 (Nov.) 1945.

Studies of the bone marrow in 12 cases of typical uncomplicated whooping cough showing the classical blood picture in the paroxysmal stage gave the following results: 1. Generally a hyperplasia in the leukopoietic system is found. 2. The myelocytes are in increased number and show a tendency to the left, especially in cases of severe disease. 3. As a rule, the eosinophils are increased even when exterior factors causing allergy cannot be found. 4. Lymphocytes are found in a normal number even in the presence of pronounced lymphocytosis of the blood. 5. The myeloic reaction remains for a rather long time and disappears only in the stage of decline. This fact was proved by a second sternal puncture in 3 of the cases studied. 6. The absence of a lymphatic reaction in the bone marrow is incompatible with the theory of a direct toxic action of Hemophilus pertussis on the lymphatic organs.

Lymphocytosis may be of central origin. The lymphocytes may be thrown out of their depots by toxic irritations of the centers of the diencephalon.

AUTHOR'S SUMMARY.

Acute Infectious Diseases

SOME EXPERIMENTAL ASPECTS OF STREPTOCOCCUS INFECTION AND RHEUMATIC FEVER. JOHN J. ROBINSON, Arch. Pediat. **62**:387 (Sept.) 1945.

A report is made of experimental studies in the attempted production of rheumatic carditis in experimental animals from which the author concluded that normal horse serum apparently injured the hearts of rabbits, rendering them more susceptible to subsequent injections of bacteria-free filtrate of streptococci. Several strains of streptococci were used, producing varying effects. A small series of young pigs were found resistant to the NY-5 streptococcus and its toxins. In none of the animals used were pathologic changes typical of rheumatic fever produced. In the opinion of the author the studies suggested the possible existence of a rheumatic virus in the causation of rheumatic fever.

GRULEE JR., Minneapolis.

SALICYLATES IN THE TREATMENTS OF RHEUMATIC PATIENT. M. B. SHELDON JR., Arch Pediat. **62**:489 (Nov.) 1945.

This report presents a general discussion and review of the leading opinions concerning the possible pharmacologic actions, the clinical administration, the absorption and excretion and the toxic effects of salicylate therapy in acute rheumatic fever.

GRULEE JR., Minneapolis.

REACTIONS TO INTRADERMAL ADMINISTRATION OF SCARLET FEVER STREPTOCOCCUS TOXIN IN RHEUMATIC CARDIAC CHILDREN. H. L. DOWD, V. P. WASSON and E. E. BROWN, Arch. Pediat. **62**:549 (Dec.) 1945.

The authors report the results of the intracutaneous administration of Veldee's tannic acid-precipitated toxin of hemolytic streptococcus (NY-5) in the prevention of recurrences of rheumatic fever among ambulatory patients. Local symptoms were generally present but not severe, and only infrequent and mild constitutional symptoms were encountered. The data reported on were included in questionnaires executed by 111 patients who received two hundred and seventy-five injections. The authors state ". . . not a single injection was followed by an attack of polyarthritis, carditis or chorea."

GRULEE JR., Minneapolis.

COMPRESSION MYELITIS DUE TO SUBPERIOSTEAL TYPHOID ABSCESS. A. SHAFIK ABBASSY, Arch. Pediat. **63**:63 (Feb.) 1946.

The author reports the case of a patient in whom after a febrile illness of one month's duration the signs of a transverse myelitis developed at the level of the

second or the third lumbar segment. Lumbar puncture revealed the presence of an abscess from which Eberthella typhosa was cultured. Extension of the spine was resorted to by the use of orthopedic apparatus and was associated with rapid onset of meningitis. E. typhosa was cultured from the spinal fluid one day before death. An autopsy was not performed.

GRULEE JR., Minneapolis.

STUDIES ON NUTRITION AND AVIAN MALARIA: IV. PROTEIN DEFICIENCY. ALBERT O. SEELER aand WALTHER H. OTT, J. Infect. Dis. **77**:181 (Nov.-Dec.) 1945.

Infections with Plasmodium lophurae were more severe in protein-deficient chicks than in chicks on a diet containing an adequate amount of protein. Not only did the parasite counts reach much higher levels in the deficient birds than in controls on a diet high in protein, but the mortality due to the disease was greater in the deficient birds. The protein-deficient chicks were unable to clear the parasites from their blood streams as readily as did chicks fed a diet containing ample protein.

TOOMEY, Cleveland.

THE CULTURING OF BLOOD CLOTS FOR BRUCELLA ORGANISMS. D. EVELYN WEST and EARLE K. BORMAN, J. Infect. Dis. **77**:187 (Nov.-Dec.) 1945.

The development of a method for routine culturing of Brucella from clots of blood specimens received for agglutination tests is described. The technic should be looked up by any one interested.

Forty cultures of Brucella abortus and 2 of Brucella suis were isolated from the clots of 4,051 routine blood specimens received for agglutination tests. Successful isolations in somewhat better than 1 per cent of specimens have resulted even though it is well established that Brucella organisms are not always present in the blood of infected persons but occur there only during "showers" from foci of infection.

The clot culture method is a valuable supplement to the agglutination test as a diagnostic aid in suspected brucellosis.

TOOMEY, Cleveland.

EXPERIMENTAL GONOCOCCAL INFECTION OF THE RABBIT'S EYE: III. TREATMENT WITH PROPHYLACTIC AND THERAPEUTIC AGENTS. C. PHILLIP MILLER, MARJORIE BOHNHOFF and VELMA MOELLER, J. Infect. Dis. **77**:216 (Nov.-Dec.) 1945.

The experimental gonococcic infection of the rabbit's eye described in the preceding communications was found to lend itself to the determination of the effectiveness of gonococcidal agents in vivo. The ocular infection was produced by injecting approximately 2×10^7 gonococci into the anterior chamber, an inoculum which produced infection in 93 per cent of the untreated controls and contained 10,000 to 100,000 times the number of gonococci required to infect 45 per cent of controls. Within one hour after inoculation, the gonococcidal agent was introduced into the anterior chamber. Twenty-four hours later the eye was enucleated, the anterior chamber rinsed with isotonic solution of sodium chloride and the lens and the ciliary body macerated and cultured. The growth of any colonies of gonococci was regarded as a failure of protection against any infection.

A number of prophylactic ointments, prepared for the prevention of venereal disease in man, were tested for their gonococcidal action. Ointments made up in aqueous (vanishing cream) base containing 15 per cent sulfathiazole or 30 per cent mild mercurous chloride or both were effective in sterilizing the anterior chamber of gonococci in all but 1 of 117 infected eyes. Similar ointments containing sulfamerazine instead of sulfathiazole were almost as effective, but those containing sulfadiazine in place of sulfathiazole were somewhat less so.

On the other hand, ointments containing sulfonamide compound and mild mercurous chloride in oily or greasy bases were found to be poor in prophylactic

activity. Their inferiority to ointments made up in aqueous bases was attributed to failure of the greasy ointments to spread and "wet" the surfaces bounding the anterior chamber.

Five and 10 per cent aqueous solutions of mild silver protein and 2 and 5 per cent solutions of strong silver protein were relatively ineffective.

Two phenylarsineoxide derivatives, p-carbamyl phenylarsineoxide and p-sulfamyl phenylarsineoxide, made up in aqueous ointments gave results indicating, respectively, 31 per cent and 53 per cent failures of prophylaxis. In oily ointments both were ineffective.

The action of penicillin on the ocular infection was studied by applying it locally and injecting it intramuscularly and intravenously. Large doses instilled into the conjunctival sac were ineffective as were repeated injections beneath the conjunctiva unless the total dose in each eye exceeded 100,000 units. Small doses, 1 unit in most instances, sufficed to sterilize the anterior chamber when penicillin was introduced directly into it.

In sharp contrast with its effectiveness when applied directly to the infected site was the failure of large doses of penicillin administered by intravenous or intramuscular injection to control gonococcic infection of the inoculated eye, indicating that the drug does not readily enter the anterior chamber from the blood stream. Interference with the mechanics of the orbital circulation by repeated aspiration of aqueous humor or conjunctival instillation of ethylmorphine hydrochloride or pilocarpine increased the therapeutic action of penicillin systemically administered.

The relative inaccessibility of the anterior chamber to penicillin intravenously administered suggests that the experimental infection here described may prove useful as a method for testing the ability of chemotherapeutic agents to destroy all susceptible micro-organisms within an animal body, i. e., to effect a genuine "cure."

TOOMEY, Cleveland.

IMMUNOGENIC POWER OF AN INTRADERMAL ANTITYPHOPARATYPHOID VACCINE. ARTURO CURBELO Y HERNANDEZ, ANTONIO CLERCH Y RIUS and ENRIQUE MARRERO Y VELA, Bol. Soc. cubana de pediat. **17**:203 (June) 1945.

The authors consider it advisable that immunization against typhoid and paratyphoid in Cuba be carried out by the intracutaneous method, although they realize that its immunologic value is somewhat less than by the subcutaneous route. They suggest three doses (0.1, 0.5 and 0.2 cc.) of a mixed polyvalent vaccine of double strength (3,000,000,000 per cubic centimeter) with annual revaccination with 0.2 cc. of the same vaccine.

KEITH, Rochester, Minn.

Chronic Infectious Diseases

STREPTOMYCIN IN EXPERIMENTAL TUBERCULOSIS. GUY P. YOUMANS and JOHN C. MCCARTER, Am. Rev. Tuberc. **52**:432 (Nov.) 1945.

In this experiment 30 white Swiss mice were given intravenous injections of 0.1 mg. of a culture of human tubercle bacilli. Fifteen animals of the group were given subcutaneous injections of streptomycin hydrochloride every six hours, a total of 3,000 units daily, for a period of twenty-eight days. The remaining animals were not treated. At the end of the experiment all but 2 of the treated animals were alive, whereas only 2 of the controls were alive. Not only did this proportion of the treated animals survive, but none lost and some gained weight.

Examination of the lungs of the control group showed extensive involvement of these organs, with gross lesions occupying an estimated 39 per cent of pulmonary substance. Gross lesions were not present in any of the treated mice. The microscopic lesions consisted only of small scattered infiltrations of peribronchial tissue

and alveoli with mononuclear phagocytes. Acid-fast bacilli were, however, present in all mice, but in considerably fewer numbers in those treated than in the controls.

The results of this experiment clearly show that streptomycin exerts a suppressive effect on experimental tuberculosis in the mouse, even though the infecting dose be large and the period of treatment relatively short. No deleterious effects were noted as a result of the treatment.

SMITH, Ogden, Utah.

TREATMENT OF PULMONARY TUBERCULOSIS WITH DIASONE. KENNETH B. OLSON, JANICE F. THOMPSON and CLARENCE J. ZINTHEO, Am. Rev. Tuberc. **52**:474 (Dec.) 1945.

One patient with minimal, 3 with moderately advanced and 6 with far advanced pulmonary tuberculosis were treated for a period of one hundred and nineteen days with Diasone (the disodium formaldehyde sulfoxylate derivative of diaminodiphenyl sulfone) in a dosage of 5 grains (0.3 Gm.) three times a day. The significant objective findings were a sharp drop in red blood cell counts and hemoglobin content of the blood followed by a gradual return to normal. There was a pronounced tendency for the sedimentation rate of all treated patients to become and remain depressed. Significant changes were not noted in the bacillary content of the sputum. Roentgenographic changes in the lungs were about the same as those in a similar group of untreated patients. It is not believed that Diasone in the dosage used and under the conditions of the experiment influenced the course of the disease beyond what may be expected of treatment with bed rest alone.

SMITH, Ogden, Utah.

A MODIFIED TUBERCULIN PATCH TEST. THOMAS C. GRUBB, Am. Rev. Tuberc. **52**:526 (Dec.) 1945.

To overcome the difficulties of the "blind" test, Grubb has developed a patch test which enables one to observe the progress of the reaction with the patch in place. A drop of undiluted old tuberculin is placed on a small square of photographic film, from which all emulsion and antihalation has been removed, and allowed to dry. This is held in place on the skin by adhesive tape with a circular window permitting observation of the reaction which may develop beneath the tuberculin-coated film. Thus it is possible to avoid missing positive reactions by too early removal of the patch, and severe reactions may be prevented by removal of the patch as soon as a positive reaction is observed. If there is any doubt as to the presence of erythema at any time, it is only necessary to apply slight pressure to the window, and if active erythema is present it fades immediately, whereas if no reaction has occurred, pressure does not alter the color of the skin.

SMITH, Ogden, Utah.

HEMORRHAGIC ENCEPHALOPATHY FOLLOWING FIVE-DAY TREATMENT OF EARLY SYPHILIS WITH MASSIVE DOSES OF MAPHARSEN (REPORT OF A CASE WITH RECOVERY). G. HEILBRUN and N. HOFFENBERG, Illinois M. J. **88**:258 (Nov.) 1945.

A survey of the literature on hemorrhagic encephalopathy during or following five day treatment with oxophenarsine hydrochloride reveals a mortality rate of only 25 per cent from that complication in contrast to a fatality percentage of 76 under the same mode of administration of other arsenicals. The relative benignancy of that complication is confirmed by the case of a 15 year old girl with early syphilis who had typical symptoms of hemorrhagic encephalopathy on the third day following completion of a five day course of treatment with a total of 1.2 Gm. of oxophenarsine hydrochloride. Final recovery was established nine days

after the onset of the cerebral incident. The role of the therapeutic agents employed is discussed and the use of high doses of ascorbic acid recommended.

BARBOUR, Peoria, Ill.

ANTIBIOTIC SUBSTANCES ACTIVE AGAINST M. TUBERCULOSIS. MILTON T. BUSH, H. L. DICKISON, CHARLOTTE B. WARD and ROY C. AVERY, J. Pharmacol. & Exper. Therap. **85**:237 (Nov.) 1945.

The gist of this highly technical report is that a strain of the mold Aspergillus flavus (Link) in culture mediums yields a substance that inhibits Mycobacterium tuberculosis, Staphylococcus aureus and Escherichia coli in vitro. The somewhat refined product is tolerated by mice and dogs in certain doses but is toxic in larger doses. The substance has not as yet been studied in experimental tuberculosis.

PILCHER, Cleveland.

TUBERCULOSIS OF THE ABDOMINAL LYMPHATIC NODES—INTESTINAL TUBERCULOSIS: PATHOGENESIS OF BOTH LESIONS. JOSE BAUZA and ALBERTO GUZMAN, Arch. Hosp. d. Niños Roberto del Rio **13**:51 (June) 1945.

This article is essentially devoted to a statistical analysis of observations at necropsy in tuberculosis of children in relation to infection of the abdominal lymph nodes. The relationship of infected abdominal nodes to infected mediastinal nodes is pointed out. By presenting the location of infected nodes in their series of cases, a cogent argument is presented for the frequent infection of the abdominal nodes from the thoracic group by retrograde flow due to stasis. In this series of 171 cases the course of events described seems to be the most frequent cause of infection, hematogenous and direct infection from ingestion being much less frequent. The authors further demonstrate the likelihood that many cases of actual ulceration of the intestinal wall itself are due to retrograde infections of the lymph. Results of experimentation with animals are presented to confirm the authors' contentions.

MILLER, Newark, Ohio.

JUVENILE PARESIS: THREE CASES. MARTIN CASTELLANOS, Bol. Soc. cubana de pediat. **17**:227 (June) 1945.

Three cases of juvenile paresis are reported in detail after a general discussion of the literature, the causes, and so forth. The three cases all showed the following features: hyperreflexia, disturbance of locomotion and speech, mental retardation, dementia and positive reactions in the blood and the spinal fluid. Of special note in the first case were hypertonicity, rapidly fatal evolution and plantar hyperpigmentation previously noted in Negroes by the author and Puente Ferro. In the second case the onset was abrupt, and slight improvement occurred following malaria therapy. In the third, improvement was noted with hyperthermia, and it was suggested the patient might be cured with penicillin, since this has opened a new horizon in the treatment of syphilis of the central nervous system, especially dementia paralytica. The author states that such cases are rare in Cuba, no previous reports having been published there.

KEITH, Rochester, Minn.

EMPHYSEMA IN TUBERCULOSIS OF THE BRONCHIAL GLANDS. H. WISSLER, Helvet. pædiat. acta **1**:147 (Nov.) 1945.

Two cases of unilateral emphysema of the lungs in the course of tuberculosis of the bronchial glands are reported. Both patients were small children. In the first case the emphysema was limited to the lower lobe and persisted several months. A benign dissemination by the way of the bronchus developed later on. In the second case the emphysema was acute and followed by atelectasis.

AUTHOR'S SUMMARY.

Diseases of the Blood, Heart and Blood Vessels and Spleen

ALEUKEMIC LYMPHATIC LEUKEMIA IN CHILDHOOD WITH SULFONAMIDE SENSITIVITY. STEPHAN EPSTEIN and STANLEY CUSTER, Arch. Pediat. **63**:57 (Feb.) 1946.

The authors present in this paper a discussion of a case of aleukemic lymphatic leukemia. Studies of bone marrow did not yield a definite and unequivocal histologic diagnosis. The association, coincidental or otherwise, of administration of a sulfonamide drug and exacerbations of the primary disease is pointed out, and the possibility of sensitivity to a drug as an etiologic factor is discussed.

GRULEE JR., Minneapolis.

PULSE-RATE AND BLOOD-PRESSURE IN INFANCY AND EARLY CHILDHOOD. G. M. ALLEN-WILLIAMS, Arch. Dis. Childhood **20**:125 (Sept.) 1945.

Pulse rates in infancy and childhood decreased with age in both sexes: In girls there was a regular decrease, while in boys there was a more abrupt fall at 2 to 3 years of age. There was greater variation between the pulse rates of sleeping children in the same age group than there was in the daily pulse rate of the individual sleeping child.

The systolic blood pressure in children of both sexes, with one exception among the girls, increased with age up to 4 years. At 4 to 5 years it declined.

At 2 to 3 years the systolic pressures in girls and the diastolic pressure in both sexes decreased. At this age period boys had a significantly higher systolic pressure than did girls.

There was a high correlation between the systolic and the diastolic pressures. There was no significant correlation between the blood pressure and the body weight in childhood.

The evidence suggests that there may be a physiologic change in the circulatory system of both sexes at 2 to 3 years of age.

KELLY, Milwaukee.

CORVISART'S DISEASE (PRESENTATION OF SEVEN NEW CASES). A. CASTELLANOS, RAUL PEREIRAS and ARGELIO GARCIA LOPEZ, Bol. Soc. cubana de pediat. **16**:329 (Sept.) 1944.

This is the association of the tetralogy of Fallot with a right-sided aorta first described by Corvisart. The authors presented the first cases diagnosed during the first few months of life at the Congress of Cardiology at Mexico City, and in a review of the literature at the time they found less than 10 cases of right-sided aorta diagnosed during life in children older than 2 years. The right-sided aorta may be present alone or associated with other cardiovascular malformations (more frequently). Once the diagnosis has been made, a complete cardiologic study must be done in a search for the congenital malformation. The authors give some notes on the embryology of the heart and the great vessels and then proceed to the presentation of 7 cases diagnosed during life when the patients were 1½ years, 4 months, 7 months, 9 years, 9 months, 22 months and 7 months old, respectively. All showed slight to intense cyanosis present from birth, 4 were poorly developed, 2 had a systolic murmur, 1 had a thrill and 1 had clubbing of the fingers. The diagnosis was made with the help of angiocardiography. A retrograde aortograph (special method devised by the authors) was also used.

In 2 of the cases the diagnosis was proved by autopsy (1 died of endocarditis; the other aspirated some water while drinking, and choked to death).

KEITH, Rochester, Minn.

SCHÖNLEIN-HENOCH SYNDROME. EMILIO ALEMAN, Bol. Soc. cubana de pediat. **17**: 498 (Dec.) 1945.

The author presents a case of a 10 year old boy with a one week history of moderate fever, malaise, headache, abdominal pain and diarrhea, slight swelling of

joints and purpuric spots especially over the extremities. Platelet count and clot retraction, prothrombin, coagulation and bleeding time were normal. There were neutrophilia and eosinophilia and the Rumpel-Leede reaction was negative. The patient was treated with moccasin venom (Lederle), and he recovered in one week.

The characteristics of the syndrome, its pathogenesis, symptoms, diagnosis and treatment, with emphasis on the allergic nature of this syndrome, are discussed by the author.

KEITH, Rochester, Minn.

ANEMIA DUE TO DEFICIENCY OF IRON. BO VAHLQUIST, Svenska läk.-tidning. **39**:2934 (Nov. 27) 1942.

Anemia due to deficiency of iron is characterized by low levels of iron in the serum, a hypochromic blood picture and satisfactory therapeutic effect with iron compounds. It is the commonest type of anemia in childhood and comprises almost all cases of secondary alimentary and postinfectious anemia and the anemia of premature infants. The anemia may be due to a deficient deposit of iron at birth, to deficient supply and deficient resorption of iron and to abnormally large losses of iron, perhaps also to an unsuitable sort of iron that cannot be used by the organism for synthesis of hemoglobin. The tendency to relapses speaks in favor of a certain constitutional predisposition. The signs and symptoms are the same as those of anemia due to deficiency of iron in adults. The normal level of iron in the serum of children (0.06 mg. per hundred cubic centimeters) decreases to 0.015 to 0.03 mg. in anemia due to deficiency of iron. During treatment with iron there is a rapid rise of the level of iron in the serum; normal values, however, cannot be expected until the hemoglobin has become normal from treatment with iron. The secondary epithelial signs may develop also in this type of anemia in children in the form of koilonychia, fissures of the lips, glabrous tongue and dysphagia. Achylia is common. The prognosis is good, although the disease predisposes to infections and lowers the general resistance of the child. It is important that large doses of iron be given for sufficiently long periods.

WALLGREN, Stockholm, Sweden.

ACIDITY OF GASTRIC SECRETION IN CHILDREN FROM BIRTH TO TWO YEARS OF AGE WITH MICROCYTIC ANEMIA. H. KREUTZFELDT and E. WINGE FLENSBORG, Nord. med. (Hospitalstid.) **13**:400 (Feb. 7) 1942.

Examination of 20 children suffering from microcytic anemia in combination with parenteral infection or diarrhea generally showed low values of acidity after ordinary test meals as well as after histamine tests. Achylia did not occur in any case. After iron medication an increase of the acidity was observed parallel to an amelioration of the blood picture, but there was no relation between the degree of increase of the hemoglobin and the acidity values.

WALLGREN, Stockholm, Sweden.

CASE OF MYELOGENOUS LEUKEMIA WITH PULMONARY INFILTRATIONS. HEDVIG ADLERCREUTZ and ASTA BERGENDAL, Nord. med. (Hygiea) **16**:2971 (Oct. 24) 1942.

A case is reported of myelogenous leukemia in a girl of 9 with roentgenologically demonstrated transient changes in the lungs which had the aspect of rounded and ultimately confluent infiltrations and which made their appearance and disappeared concomitantly with the deterioration and the improvement of the blood picture. There was no postmortem examination. The authors are of the opinion that the pulmonary changes in this case are of the same type as in the case reported by Joachim and Loewe (*Am. J. M. Sc.* **174**:215, 1927); namely, infarct of the lung produced by thrombosis of the pulmonary vessels by myelogenous cells.

WALLGREN, Stockholm, Sweden.

SPLENOGENIC MALIGNANT LEUKOPENIA, THROMBOPENIA AND ERYTHROPENIA. PER SELANDER, Nord. med. (Hygiea) **16**:3565 (Dec. 19) 1942.

A girl of 11 had had petechiae on the skin from the time that she was 2 years old. At the first examination, when she was 7, she was anemic (the hemoglobin

value was 32 per cent, there were 1,400,000 erythrocytes and 3,000 to 4,000 leukocytes, with as few as 1,000 to 1,500 leukocytes (15 to 25 per cent granulocytes). A sternal puncture showed a normal picture. A splenectomy was performed with rapid improvement of the girl's condition and normal blood values. The author cites 6 similar cases previously reported on by various authors.

WALLGREN, Stockholm, Sweden.

Diseases of Nose, Throat and Ear

PREVENTION OF DEAFNESS IN CHILDREN. RUSSELL M. DECKER, Ann. Otol., Rhin. & Laryng. **54**:358 (June) 1945.

The United States Children's Bureau states that a minimum of 2 per cent of all school children are hard of hearing. Prevention is important, and the primary causes of deafness in childhood are pathologic changes occurring (1) in the middle ear, (2) in the eustachian tube and (3) about the tubal orifice. In the middle ear the drumhead may be thickened, perforated or distorted by adhesions. The ossicular chain may be involved by granulations, necrosis and disarticulation. Edema of the mucosa may be inflammatory or allergic. The eustachian tube shares the inflammatory processes of the nose and the throat. There is tubal involvement associated with allergic, as well as with inflammatory, conditions of the nose and the throat. Strictures may occasionally develop. About the tubal orifice the hypertrophic adenoid is the most important predisposing cause, though the size is not so important as the location, those close to the tubal orifice being more dangerous than those hanging free from the pharyngeal vault. Tonsils involve the hearing either by obstructing the tube or by constantly transmitting infection to it, so that the small tonsil may be as great a menace as the large, depending on the amount of infection present. Nasopharyngeal discharge of pus and new growths may involve the tube. Early diagnosis of the trouble is important.

M. V. MILLER, Philadelphia. [ARCH. OTOLARYNG.]

TESTING THE HEARING OF YOUNG CHILDREN. EMIL FROESCHELS, Arch. Otolaryng. **43**:93 (Feb.) 1946.

The audiometer, although superior in testing the hearing of older children, is inapplicable with young children and infants. The author has seen tests made with the audiometer on children up to 8 years of age indicate complete deafness, but the same children show reactions to tones introduced directly into the ear by a rubber tube attached to an "ear olive" inserted into the ear. The technic of examination is recorded and remedial work outlined. If hearing is demonstrable, stimuli should be introduced into the ear of the child with the help of a hearing tube. The stimuli should consist of musical sounds, noises, single speech sounds and later on, words and increasingly longer phrases. The spontaneous development of speech could be brought about in at least a number of partially deaf children in this way.

KIMBALL, Evanston, Ill.

TREATMENT OF ACUTE PHARYNGEAL INFECTIONS BY INSUFFLATION OF SULFANILAMIDE POWDER. JOSEPH L. GOLDMAN and W. B. KIESEWETTER, Arch. Otolaryng. **43**:99 (Feb.) 1946.

Thirty-two patients with acute pharyngeal infections were treated with insufflations of sulfanilamide powder once or twice each day. The average length of time required for clinical cure was 1.8 days shorter than for an equal number of control patients treated in the standard ways; i. e., with hot saline gargles and irrigations. Twenty-eight patients with Vincent's ulcerative tonsillitis were treated by insufflations of sulfanilamide and cured 1.7 days faster than 23 patients used as controls treated with sodium perborate, half strength hydrogen peroxide gargles and, in 8 cases, a single injection of oxophenarsine hydrochloride. About 5 grains (0.3

Gm.) of sulfanilamide powder was insufflated with either an air-compressed or a hand-compressed De Vilbiss glass powder blower once a day in the early part of the series and twice a day in the latter part of the series. Nine patients with acute pharyngitis were similarly treated, but no conclusions are drawn.

KIMBALL, Evanston, Ill.

BISMUTH SALICYLATE IN OIL: THE TREATMENT OF CHOICE IN VINCENT'S ANGINA. HARRY D. GROSSMAN, Illinois M. J. **89**:28 (Jan.) 1946.

Of 150 patients treated with bismuth subsalicylate in oil given intramuscularly, 10 per cent required three injections before the lesions disappeared completely; the others all had two injections forty-eight to seventy-two hours apart. The patient is usually much relieved within twenty-four hours after the first injection. The first dose is 1.5 cc. (2 grains). The second and subsequent doses are 2 cc. (4 grains) each. The treatments are given deep in the buttocks alternately.

BARBOUR, Peoria, Ill.

DYNAMIC FACTORS IN THE MOTOR-KINESTHETIC METHOD OF SPEECH CORRECTION. W. ARTHUR CABLE, Quart. J. Speech **31**:350, 1945.

Cable studied the work of Mrs. Edna Hill Young during the second term of the 1943 summer session of the University of Denver Speech Clinic. The following conclusions were reached: 1. The motor-kinesthetic method of developing and correcting speech consists primarily of dynamic concepts, principles and procedures. 2. Neuromuscular learning is at the vortex of the motor-kinesthetic method. 3. The motor-kinesthetic method of correction is centered on muscle movement and allied dynamic factors. 4. The dynamic factor of energy, in terms of muscular force, is recognized and utilized as an essential. 5. Those who learn this method are taught to recognize and build toward the integration of the total organism as an instrument of speech 6. The dynamic content of this method appears to be the primary cause of its superiority over the visual-auditory method. 7. The employment of motivation by the correctionist or the clinician is vital. 8. The method under consideration is a striking application of the educational principle that all learning should be acquired through activity of the learner. Two illustrative cases are presented.

PALMER, Wichita, Kan. [ARCH. OTOLARYNG.]

LARYNGOTRACHEOBRONCHITIS. CARLOS HERRERA and GENARO GONZÁLEZ B., Bol. méd. d. Hosp. inf., México **2**:367 (Jan.-Feb.) 1946.

This report is a review of the authors' experience from July 1943 to October 1945 at the Hospital del Niño. After a careful selection, 23 cases of laryngotracheobronchitis were verified. The authors find that the incidence is greater in the cold months. A greater number of cases is found in children not yet of school age. This disease cannot be attributed to a specific germ. The authors believe that bronchoscopy is essential in the differential diagnosis. Other diseases with which it may be confused are laryngeal diphtheria and foreign bodies in the larynx and the trachea. A detailed description of the symptoms is given. The therapeutic measures followed at the Hospital del Niño are described in detail, and statistics are given. The authors also point out the management of the emergency cases. The progress is discussed.

MADERO, México, D. F., Mexico.

Diseases of Lungs, Pleura and Mediastinum

CONGENITAL CYSTIC LUNG. ROBERT E. GROSS, Ann. Surg. **123**:229 (Feb.) 1946.

Congenital cysts of the lungs are less common than the acquired form. If they do not become infected and if they are small enough to leave the functioning of the lung undisturbed, they are of little clinical significance.

However, they may give rise to complications, principally of two sorts. In the first, infection of the wall of the cyst or suppuration within its lumen may be extensive and serious. In the second, the cyst is connected to the respiratory tract by a relatively small passageway, so that air enters and becomes entrapped within the cavity. Thus the cyst becomes greatly distended and compresses adjacent pulmonary tissue, and respiratory distress can be extreme.

Respiratory embarrassment from increased tension within pulmonary cysts could be relieved in one of several ways: 1. A needle can be passed through the wall of the chest and into the cavity of the cyst to withdraw entrapped air. 2. A trochar may be introduced through the wall of the chest and into the wall of the cyst so that a catheter may be threaded into it for establishment of prolonged aspiration. 3. Marsupialization of the cyst onto the wall of the chest and destruction of its lining membrane may be done. 4. The cyst may be enucleated or the pulmonary tissue containing it removed.

The author considers the last method the treatment of choice and reports the successful treatment of a congenital cyst in a 3 week old baby by total pneumonectomy.

BANTIN, Omaha.

PNEUMONIA DUE TO STREPTOCOCCUS VIRIDANS: REVIEW OF LITERATURE AND CASE REPORT. JOHN B. REINHART and W. L. VENNING, J. Pediat. **27**:480 (Nov.) 1945.

Alpha streptococcus as an important causal agent in pneumonia is discussed, and the few cases attributed to this organism are reviewed and presented in a graphic chart.

The diagnosis of pneumonia due to alpha streptococcus is not simple, and mere observation of the organism in a culture of sputum is not sufficient, though cultures containing only this organism or containing it predominantly are suggestive. Such cultures should stimulate a search for the organism in blood and pleural fluid, particularly in the atypical pneumonias.

Streptococcus viridans pneumonia clinically resembles so-called atypical pneumonia and does not respond to chemotherapy. Clinically also, intense pleural pain was noted in a number of the cases. Morbidity and mortality are high, with hospital stays of fifteen to sixty days reported for those recovering and a fatality rate of 50 per cent in those cases reviewed. The majority of the cases reviewed were lobar in type, and pathologically an intense, purulent bronchiolitis was the chief finding; no cardiac lesions were found. The age of the patients ranged from 13 to 82 years in the 16 cases reviewed.

The case presented is of a 7 month old white girl who had bronchopneumonia with cultures containing Streptococcus viridans from the throat, the blood and the pleural fluid. She was treated with sulfadiazine and penicillin, and in vitro studies of the organism were made. Recovery finally ensued. Sulfonamide compounds were given no credit for the favorable course of the disease, and the effect of penicillin was deemed questionable. This is believed to be the youngest patient reported to have this disease and the first time that penicillin had been used in its treatment.

AUTHORS' ABSTRACT.

DYSECTASIS PULMONUM. ERICH NASSAU, Ann. pædiat. **165**:312 (Dec.) 1945.

Atelectasis and compensatory emphysema are described and illustrated by some typical examples. These conditions were given more attention in older pediatric literature than they are now.

Aspiration of foreign bodies, mucus, blood, liquor amnii, food particles, cod liver oil and liquid petrolatum plays an important part in the causation. Atelectasis may also be caused by compression of the bronchi (tuberculous or otherwise infected glands, neoplasms). Other causal factors are invasion by tuberculous

tissue, abdominal pains or abdominal operations (interference with diaphragmatic movements) and, finally, venous congestion in the pulmonary circulation. Atelectasis may further be produced by a paralysis of respiratory muscles during poliomeylitis.

There is a discussion of clinical diagnosis, mechanical pathogenesis and relationship with other pulmonary diseases such as emphysema, pseudoabscess, spontaneous pneumothorax and bronchiectasis.

AUTHOR'S SUMMARY.

ATELECTASIS OF THE RIGHT LUNG DUE TO FOREIGN BODY. A. AGUIRRE, Bol. méd. d. Hosp. inf., México **1**:35 (March) 1944.

R. M. S., an 11 month old boy, was admitted to the hospital because of cough, dyspnea and fever. The illness began five days previously with a sudden attack of cough and asphyxia. Later there were some cyanosis and dyspnea. Two days afterward the fever began; it was continuous. Clinically and roentgenologically atelectasis of the right lung was diagnosed. A foreign body (tamarind seed) was removed from the right bronchus by the bronchoscopist. A steam tent, transfusions and sulfadiazine, 0.25 Gm. every four hours, were ordered. The recovery was more or less uneventful and was complete in less than five days.

MADERO, México, D. F., Mexico.

AN ATTEMPT TO DELINEATE THE NORMAL IMAGE OF THE LUNGS IN CHILDREN. FEDERICO GÓMEZ and LUIS VARGAS Y VARGAS, Bol. méd. d. Hosp. inf., México **2**:337 (Jan.-Feb.) 1946.

In this paper the authors attempt to determine the normal image of the lungs in children from prematurity to puberty. They base their assertions exclusively on the experience acquired at the Hospital del Niño in over two years of practice, since they have not found any publication on this subject.

They first describe the technic used in the roentgenologic department of the hospital. A description of the elements found in the roentgenograms comes next, and then a detailed interpretation of what they consider normal roentgenograms of the chest for children at different ages: They describe the normal roentgenogram of the chest of the premature infant, of the 1 year old infant, of the 3 year old child and of the child of 5, 8, 11 and 13 years.

MADERO, México, D. F., Mexico.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

CONGENITAL HYPERTROPHIC PYLORIC STENOSIS: REVIEW OF THIRTY CASES. A. N. CONTE and J. T. MCNALLY, Arch. Pediat. **63**:1 (Jan.) 1946.

Beginning with a short historical review the authors discuss a series of 30 patients with congenital hypertrophic pyloric stenosis treated during 1943. Twenty-nine patients were ultimately managed surgically with a 3.8 per cent mortality. Pyloric tumors were encountered in each patient operated on. Preoperative medical treatment of various types was attempted in some cases. Postoperative care was briefly mentioned with particular reference to the occurrence of postoperative vomiting. In this connection the authors feel that a fast of more than fourteen hours may be indicated in order to insure that gastric peristalsis has been restored prior to oral feeding.

GRULEE JR., Minneapolis.

SURGICAL TREATMENT OF CONGENITAL ATRESIA OF THE ESOPHAGUS. CONRAD R. LAM, J. Pediat. **27**:456 (Nov.) 1945.

The congenital atresias of the esophagus have been classified by E. C. Vogt as follows: In type 1 there is complete absence of the esophagus (rare). In type 2

there are an upper and a lower segment ending in blind pouches (also rare). In type 3 one or both of the segments communicate with the trachea or a bronchus. This type is subdivided into type 3 (*a*), in which the fistula is between the upper segment and the trachea; type 3 (*b*), in which the fistula is between the lower segment and the trachea, and type 3 (*c*), in which both segments communicate. Type 3 (*b*) is the commonest, accounting for 80 to 90 per cent of all atresias of congenital origin.

If a newborn infant has a tendency to choke on its own mucus or is unable to take water or feedings, suitable roentgen studies should be carried out after the passage of a catheter into the esophagus. Typically, the catheter will be observed to stop at the level of the second thoracic vertebra. A little iodized oil introduced into the catheter will outline the blind pouch. Air in the gastrointestinal tract indicates that there is a fistulous connection between the lower segment and the trachea.

The ideal operative procedure is one which restores the normal anatomy through a mediastinal approach. Such an operation was attempted unsuccessfully by Robert Shaw in 1938 and with success by Cameron Haight in 1941. Including the two cases described in this paper, the literature contains reports of 13 babies who are alive and well after the operation. Most or all of the operation is performed under local anesthesia. Access to the mediastinum is gained by exposure of the vertebral ends of all ribs from the second through the sixth, subperiosteal resection of short lengths of these ribs, section of the third, fourth and fifth intercostal bundles and careful reflection of the parietal pleura from the vertebral column. It is necessary to ligate the azygos vein on the right or the upper two or three intercostal arteries on the left to open up the space behind the trachea where the distal segment will be found. Approach, therefore, may be from either the right or the left side. The upper segment is identified by the palpation of a catheter which has been introduced through the mouth. An opening is made in the upper pouch, and end to end anastomosis to the lower segment is carried out after the latter has been ligated close to the trachea and cut. The catheter over which the anastomosis is done is removed, and the muscles and the skin closed about a drain. The infant is fed parenterally for five days, after which cautious feeding is begun.

The author has recently operated on 2 infants according to the method just described. Both were on unrestricted formula feedings after the tenth post-operative day. There has been normal gain in weight during the ensuing months.

Another child is alive and well following a multiple stage procedure in which double gastrostomy and cervical esophagostomy were done early, to be followed by intrapleural ligation of the distal segment with exteriorization. After several disappointments, an antethoracic cutaneous tube to connect the two esophagostomies is practically completed.

There are 15 patients alive after the multiple stage procedure, but only two external cutaneous tubes have been completed.

In case 4 of the author's series a short upper segment made anastomosis impossible, and after the unsuccessful operation the child died with pneumonia and atelectasis. The recovery rate, therefore was 3 of 4.

AUTHOR'S ABSTRACT.

CONGENITAL MEGACOLON. M. G. PETERMAN, J. Pediat. **27**:484 (Nov.) 1945.

The causation of this disease has remained an enigma. There are probably many cases of moderate dilatation which remain undiagnosed for years even though the constipation or obstipation is persistent or severe. The surgical treatment of the disease is hazardous and unsuccessful. The medical treatment with acetyl-beta-methylcholine bromide is highly successful and is perfectly safe. The initial dose of the drug is 50 to 200 mg. before or after breakfast followed in two hours

by an enema. Liquid petrolatum is given every night to keep the stool soft. After a definite time for evacuation is established the enema may be discontinued and a suppository used when necessary. When a satisfactory diet has been established the liquid petrolatum may be gradually reduced and then discontinued. Finally the amount of acetyl-beta-methylcholine bromide is gradually reduced, and, if possible, administration of the drug is discontinued. Eight cases are presented and the lesions are illustrated with roentgenograms. The patients ranged in age from 14 months to 9½ years. Two patients had had colostomies with no relief and 1 child had had a lumbar sympathectomy without relief.

AUTHOR'S ABSTRACT.

PNEUMOCOCCIC STOMATITIS. CARL J. OCHS, J. Pediat. **28**:481 (April) 1946.

The growth of pneumococci primarily in the mouth is not generally recognized. A review of the literature for the past twenty years reveals one article only in which the author, Crawford, recorded 9 cases which he had observed. Textbooks on pediatrics and on diseases of the mouth do not apparently recognize the condition, although Griffith and Mitchell stated that a pseudomembrane may be produced in the mouth by the pneumococcus, perhaps in the course of pneumonia. If the condition is as unusual as is indicated by the textbooks and the literature the report of this case seems indicated.

A boy was 5 weeks of age when first seen. His mother had observed white patches in his mouth which she assumed to be particles of milk. The mouth appeared to clear following the local application of gentian violet medicinal. Later white patches in the mouth appeared, but in spite of repeated applications of gentian violet medicinal, the mouth became gradually worse. The lesions were located on the buccal mucous membranes, on the gums, both above and below, on the margin of the tongue and beneath the tongue. The membrane was thin, translucent and firmly adherent. The mucous membranes bled freely when the membrane was removed. There was no induration of the surrounding mucous membrane There was no detectable odor.

Gentian violet medicinal applied locally was not effective. When penicillin, 250 units to the cubic centimeter, was applied locally every two hours in addition to the gentian violet medicinal, the baby appeared to be worse. Penicillin was then given intramuscularly, 3,000 units per cubic centimeter every three hours. The patient appeared to be critically ill, and for that reason sulfadiazine, 1 grain per pound (132 mg. per kilogram) daily, was also given.

On January 20 the culture taken from the membrane in the mouth January 18 was reported positive for type XIV pneumococcus. A roentgenogram of the chest did not show any pathologic condition to be present. On the following day oxygen was administered because of an apparent tracheobronchitis.

The temperature of the patient at no time exceeded 101 F.

AUTHOR'S ABSTRACT.

IDIOPATHIC MUSCULAR HYPERTROPHY OF OESOPHAGUS, PYLORUS, DUODENUM AND JEJUNUM IN A YOUNG GIRL. KATHARINE J. GUTHRIE, Arch. Dis. Childhood **20**:176 (Dec.) 1945.

An unusual case is reported of symptomless idiopathic and possibly congenital muscular hypertrophy of the esophagus, the pylorus, the duodenum and the jejunum in a child.

KELLY, Milwaukee.

THE TREATMENT OF POST-IRRADIATIONAL ULCERS BY RADON OINTMENT. A. G. S. COOPER and D. F. ROBERTSON, M. J. Australia **1**:297 (March 24) 1945.

The authors report excellent results in the treatment of post-irradiational necrotic ulcers (except those due to gross overdosage), roentgen dermatitis, varicose ulcers,

chronic ulceration occurring in thermal burns and keloids by the use of radon-impregnated petrolatum as outlined by Uhlmann (*Radiology* **38**:445 [April] 1942). Radionecrotic ulcers most commonly appear many months after recovery from the original condition treated by irradiation and are not a direct sequel to irradiation but a result of the inadequate blood supply of scar tissue. In such cases as well as in all scar tissue necrosis the radon ointment of low strength stimulates and promotes the growth of vascular epithelial tissues.

GONCE, Madison, Wis.

REGIONAL ENTERITIS: TERMINAL ILEITIS, CROHN'S DISEASE. ERWIN SCHIFF, Ann. pædiat. **165**:281 (Dec.) 1945.

Regional enteritis is sometimes observed in children. It is important therefore that the pediatrician know about the disease, all the more so because regional enteritis has some features shared with some other diseases in children and can therefore be easily mistaken for these diseases. The clinical picture, the pathologic changes, the diagnosis and the treatment of regional enteritis are described and 1 typical case of his own is presented by the author.

AUTHOR'S SUMMARY.

PURULENT STREPTOCOCCIC PERITONITIS OF THE NEWBORN INFANT: RECOVERY WITH SULFONAMIDE THERAPY. P. ROHMER and J. A. ROHMER, Arch. franç. pédiat. **3**:67, 1946.

The infrequency of recovery in such cases warrants this report. An infant of 7 weeks, living under deplorable hygienic conditions, had fever with anorexia. Examination revealed fine rales at the base of the right lung and along the spine; there was great abdominal distention with liquid stools but no vomiting. On admission to the hospital, about the third or the fourth day of fever, the baby's temperature was 37.7 C (99.86 F.); it was exhausted and the expression was anxious. Intumescence of the abdomen had increased, and there was tympany on percussion. Puncture on the following day produced thin greenish pus under considerable pressure. Smears revealed streptococci and enterococci. One could then palpate readily. The liver was found moderately enlarged, and the spleen was palpable; there was no induration about the umbilicus.

Intensive treatment with sulfonamide drugs was instituted; 1.25 Gm. of sulfathiazole was offered daily. Breast milk was procured and fed in increasing amounts until the infant was able to take the breast. A further puncture, on the sixth day, withdrew 20 cc. of pus showing rare colonies of the streptococcus, while subsequent paracenteses revealed a gradually diminishing growth until the small quantity of fluid removed on the fifth was sterile. The initial dose of sulfonamide drug was maintained for six days and then gradually reduced to the thirty-first day. A total of 20 Gm. was used in twenty-six days.

AMESSE, Denver.

A POSTMORTEM STUDY OF A CASE OF INTESTINAL APLASIA. MAXIMILIANO SALAS, Bol. méd. d. Hosp. inf., México **2**:387 (Jan.-Feb.) 1946.

G. H. J., a 6 day old boy, was admitted to the surgery ward because of enlargement of the abdomen since the day after birth, dark-colored projectile vomiting and bloody mucus, in scant quantity, through the rectum.

The author's main observations were as follows: The duodenum was 12 mm. in length, and from it the small intestine began to widen until it reached a diameter of 60 mm.; at that point it abruptly formed a cul-de-sac. A portion of about 2 cm. of the intestine was then missing, being replaced by a fold of the mesentery. There was then another blind pouch. From that point on the intestine was extremely narrow (4 mm.) without a perceptible cavity; it continued like that until its termination at the cecum.

MADERO, México, D. F., Mexico.

NOMA, APPEARING SIMULTANEOUSLY IN THE MOUTH, VULVA AND ANUS. GUSTAVO CARDELLE, FRANCISCO DUCASSI and D. RODRIGUEZ, Bol. Soc. cubana de pediat. **17**:240 (July) 1945.

Noma is a rare disease, and it is still more rare to have the lesions simultaneously in the mouth, the vulva and the anus. The authors report 1 case in detail and mention 1 other case of noma of the face. Most cases occur in the summer or fall, the majority in female patients. Bacteriologic studies showed mixed flora, as usual. Noma is considered to be a toxic form of ulcerative stomatitis. In the authors' case the process began in the mouth, extended to the face and later to the vulva and the anus. The absence of toxic signs, fever and leukocytosis with good general condition indicated a localized process. The patient recovered after local treatment with 10 per cent chromic acid, alternating with 10 per cent arsenic in glycerin, and systemic treatment twice weekly with sulfarsphenamine intramuscularly up to a total of 0.5 Gm. per kilogram of body weight. Transfusions and general therapeutic measures were also used. There is an extensive, general discussion of the subject.

KEITH, Rochester, Minn.

POSSIBLE RELATION BETWEEN VITAMIN E AND HYPERTROPHIC PYLORIC STENOSIS. FONSECA E. CASTRO, Rev. españ. pediat. **1**:646 (Sept.-Oct.) 1945.

The author presents a case of probable pyloric stenosis, although the tumor was not felt, in which the administration of vitamin E was successful. He feels that lack of this vitamin, by changes in neuromuscular synapses, might lead to pyloric stenosis or at least to pylorospasm.

MILLER, Newark, Ohio.

SOME PICTURES OF THE PATHOLOGY OF THE PANCREAS. C. DE LANGE, Maandschr. v. kindergeneesk. **13**:1 (Oct.-Nov.) 1943.

Four cases of congenital cirrhosis of the pancreas in babies are reported, 3 of which came to autopsy. The clinical picture greatly resembles that of atrophy ("decomposition" in the terminology of Finkelstein), but pulmonary processes and a permanent cough are more prominent in these cases. Besides congenital cystic cirrhosis of the pancreas noncystic cirrhosis was observed. In the noncystic cirrhosis alterations of the islets of Langerhans were found.

Further, the history is reported of an infant who died on the fifth day after birth; the mother had diabetes. Besides hypertrophy of the islets of Langerhans in the pancreas, a hemorrhage of the left adrenal gland was found. The author recommends that the quantity of insulin which is administered to the mother during the later months of the pregnancy be not diminished, as this would give rise to an increased activity and hypertrophy of the islets in the child's pancreas.

VAN CREVELD, Amsterdam, Netherlands.

HIATUS HERNIA BRACHYESOPHAGEA IN A BABY. F. A. BANNINK, Maandschr. v. kindergeneesk. **13**:127 (April) 1944.

A case of shortened esophagus in an infant 2 months old is reported. Fluoroscopic examination with opaque meal is recommended in all cases of frequent vomiting in infants. A terminology for the classification of the group of hiatal hernias as given by Åkerlund (1926, 1933) is discussed.

VAN CREVELD, Amsterdam, Netherlands.

ACUTE ABDOMINAL SYMPTOMS WITH CONGENITAL ANOMALIES. E. MEERMAN-SCHRÖDER, Nederl. tijdschr. v. geneesk. **87**:630 (April 3) 1943.

The case histories are given of 3 children with congenital anomalies of the mesentery, which caused acute abdominal symptoms. The origin of these anomalies

is briefly discussed, and stress is laid on the importance of the fold of Treves with respect to the formation of mesenteric defects. A fourth child had an extremely large diverticulum of Meckel, the walls of which were completely lined with gastric mucosa. Acute abdominal symptoms were present in this case also.

VAN CREVELD, Amsterdam, Netherlands.

PROLAPSUS ANI ET RECTI IN YOUNG CHILDREN. R. J. HARRENSTEIN, Nederl. tijdschr. v. geneesk. **87**:788 (April 24) 1943.

The author reports on the different forms of prolapsus ani et recti and stresses the greatly increasing frequency of these defects during the years of the war. He discusses the means of obtaining the normal condition along conservative lines; if these means prove insufficient he recommends the operation according to Ekehorn (1909) in a modified form.

VAN CREVELD, Amsterdam, Netherlands.

Psychology and Psychiatry

THE CRYING OF NEWLY BORN BABIES: III. THE EARLY PERIOD AT HOME. C. ANDERSON ALDRICH, CHIEH SUNG and CATHARINE KNOP, J. Pediat. **27**:428 (Nov.) 1945.

Forty-two infants were observed in their homes with the cooperation of their mothers during the first few weeks after their return from the nursery for newborn infants in the hospital.

The average baby at home had 4.0 prolonged episodes of crying per day as opposed to 11.9 prolonged episodes of crying in the hospital nursery. The causes given for crying differed somewhat under home observation; hunger clearly led as a cause and unknown reasons appeared to be a much less frequent cause than in the hospital nursery. Wet diaper, soiled diaper and vomiting remained in the same order as causes of episodes of crying. Many babies seemed to cry during their daily bath. Hot weather, noise and light were minor reasons for crying.

The conclusion was that, since young babies showed fewer crying spells when given individualized care at home, increasing the individual attention of babies in the hospital should reduce their difficulties.

AUTHORS' ABSTRACT.

THE PSYCHODYNAMICS OF THE ART EXPRESSION OF A BOY PATIENT WITH TIC SYNDROME. MARGARET NAUMBURG, Nervous Child **4**:374, 1944-1945.

This is an excellent detailed article describing the artistic creations of an 11 year old boy who was under treatment for tics. This patient is one of a series who are being encouraged to draw at the New York State Psychiatric Institute in order to investigate the possible use of creative art as an aid in diagnosis and therapy. The drawings which are presented and the objective observation made by the writer are of great value and interest. This work is one of many possible types of psychotherapy which can be used with normal and psychiatric patients.

BEVERLY, Oak Park, Ill.

Diseases of the Genitourinary Tract

DYSMENORRHEA AND PHYSICAL EDUCATION. F. SCHUCK, Arch. Pediat. **63**:8 (Jan.) 1946.

This article constitutes a discussion in general terms and without bibliography of the problem of dysmenorrhea as encountered in educational and industrial programs. Various medical and psychologic aspects of the problem are described with particular emphasis on psychologic conditioning. In the opinion of the author dysmenorrhea not attributable to definite pathologic conditions in the pelvis can

best be handled by deemphasizing the menstrual phenomenon with respect particularly to sports and physical education. At the same time he recognizes the need of individual medical management in appraising both physical and psychologic thresholds.

GRULEE JR., Minneapolis.

THE PROGNOSIS IN ACUTE GLOMERULONEPHRITIS IN CHILDREN. JOSEPH H. DAVIS and HAROLD K. FABER, J. Pediat. **27**:453 (Nov.) 1945.

A series of cases of acute glomerulonephritis observed at Stanford University School of Medicine, studied by the Addis technic and followed for adequate periods of time from the onset, has been analyzed by the authors. They excluded all cases not seen in the initial stage, thus avoiding certain important factors of selection and weighting inherent in the inclusion of patients referred to the clinic during later stages of the disease. Such weighting has been responsible for the apparently poor prognosis found in some earlier studies.

Of the 102 patients in the present series, 83 (81.3 per cent) recovered; 8 (7.8 per cent) still had active lesions after two years; 6 (5.9 per cent) died during the initial stage, and 5 (4.9 per cent) died of chronic nephritis. Of the 96 that survived the initial stage (acute nephritis), 86.5 per cent recovered completely; 8.3 per cent still had active lesions for more than two years (such patients rarely recover), and 5.2 died of chronic nephritis.

The prognosis in the series is therefore much better than that found by some writers but does not justify the opinion expressed by others that the outlook is uniformly good for those patients who survive the initial attack, since 13.5 per cent of the authors' patients went on to chronic nephritis and had either died of it already or had little chance of eventual recovery.

AUTHORS' ABSTRACT.

EFFECTS OF DIIODOTYROSINE AND VITAMIN E ON CREATINURIA: EXPERIMENTAL STUDIES IN MAN AND ANIMALS. HANS CHRÉTIEN, Ann. pædiat. **163**:225 (Dec.) 1944.

Creatinuria caused by thyroxin in children can be suppressed equally well by means of diiodotyrosine and of vitamin E. Creatinuria caused by oral administration of creatine in children may also be got rid of by use of diiodotyrosine and vitamin E. Creatinuria in rabbits set up by administration of tri-ortho-cresylphosphate is not affected by diiodotyrosine; it is, however, affected by vitamin E. The general conclusion may be drawn that in the effects of diiodotyrosine and vitamin E on creatinuria two different mechanisms seem to be active.

AUTHOR'S SUMMARY.

A CASE OF CYSTINE STORAGE WITH RENAL DWARFISM AND RICKETS. ROBERT LOOSER, Ann. pædiat. **163**:251 (Dec.) 1944.

The author reports the anatomicopathologic results of a case of cystine disease and cites 10 cases described in the literature. The presence of cystine was chemically proved. It was present in the cells of the whole reticuloendothelial system, especially in the lymph nodes, the spleen, the liver and the kidneys. The storage of cystine and cystinuria are mutually exclusive. Necrotic changes were present in the liver and the spleen. This pathologic condition was due to metabolic disturbances plus changes in the kidney. Prominent among these were hyaline sclerosis of the glomeruli, which is primary and which is followed by tubulonephrosis and an infiltration of lymphocytes in the connective tissue. These changes show a relationship to those which are found in diabetes by Kimmelstiel and Wilson. There was severe rickets with pronounced fibrosis of the marrow, which may be partly traced back to renal insufficiency. The dwarfism was due to a combination of various disturbances, possibly to a predominating defect in the metabolism of cystine.

AUTHOR'S SUMMARY.

CANCER OF THE TESTICLE IN AN INFANT OF NINE MONTHS. J. LEVEUF, Arch. franç. pédiat. **2**:209, 1944-1945.

At a regular session of the Pediatric Society of Paris held on January 16, 1945, the president, Professor J. Leveuf, presented the patient. When the infant was at the age of 3½ months a tumor of the scrotum developed. At first considered a hernia, it offered some of the characteristics of hydrocele, but the results of puncture were negative. Investigation then revealed a malignant tumor which proved to be a canalicular cancer of the wolffian type.

AMESSE, Denver.

SARCOMA OF THE PENIS IN A CHILD OF TWO YEARS. L. LEVEUF, Arch. franç. pédiat. **2**:209, 1944-1945.

At the age of 6½ months, a child presented a tumor on the dorsal surface of the penis. Biopsy permitted the diagnosis of fibroplastic sarcoma. The neoplasm having the same consistency throughout, amputation, followed by irradiation, was obviously the only treatment considered. The patient was still under observation.

AMESSE, Denver.

Diseases of the Ductless Glands; Endocrinology

AN EVALUATION OF LABORATORY METHODS USED IN THE DIAGNOSIS OF CERTAIN ENDOCRINE DISORDERS IN CHILDREN. SOL LEVY, Arch. Pediat. **62**:437 (Oct.) 1945.

The author reports the results of determinations of cholesterol in the serum and of basal metabolic rates and tests of dextrose tolerance performed on 100 children manifesting various endocrinopathies including hypopituitarism of the Fröhlich and the Lorain-Levi type, hypergonadism and pluriglandular involvement. The values determined by these tests were compared with those obtained for a group of 100 normal children. It was concluded from the study that the determination of cholesterol in the serum is the most helpful and reliable method for the diagnosis of endocrine conditions in children. The basal metabolic rate was considered of questionable value and the dextrose tolerance test essentially useless.

GRULEE JR., Minneapolis.

GOITROGENIC AGENTS AND THYROIDAL IODINE: THEIR PHARMACODYNAMIC INTERPLAY UPON THYROID FUNCTION. W. T. SALTER, R. E. CORTELL and E. A. MCKAY, J. Pharmacol. & Exper. Therap. **85**:310 (Dec.) 1945.

The thyroid glands of white rats were depleted of iodine by adding 150 mg. of thiouracil and 13 micrograms of iodine to their daily diet. After twenty-three days iodine (or another drug) was added to the diet. The iodine content of the thyroid was determined in some of the rats. It was found that iodine was not trapped. In part the deficiency could be overcome by larger doses of iodine, but the conversion of iodine to diiodotyrosine (and to thyroxine) was prevented.

PILCHER, Cleveland.

URINARY EXCRETION OF ESTROGENS AND 17-KETOSTEROIDS IN YOUNG, ADULT MALES WITH INFECTIOUS HEPATITIS. HELENA GILDER, and CHARLES L. HOAGLAND, Proc. Soc. Exper. Biol. & Med. **61**:62 (Jan.) 1946.

Inasmuch as male subjects with chronic disease of the liver are known to have symptoms such as testicular atrophy, gynecomastia, decrease in total body hair, development of spider telangiectasia and loss of libido which may well be due to increase in estrogenic substance, the authors studied the urinary excretion of estrogens and 17-ketosteroids in 11 male subjects with acute infectious hepatitis.

In the 2 cases of mild disease no significant changes in the urinary excretion of the estrogens occurred. In the 9 cases of moderately severe disease there was a significant elevation in the level of the excretion of biologically active estrogens in the urine which persisted, decreasing gradually until convalescence. The urinary excretion of 17-ketosteroids was markedly to moderately depressed early in the course of acute hepatitis with a rather rapid return to normal with clinical recovery.

HANSEN, Galveston, Texas.

CUSHING'S SYNDROME IN A BOY THREE AND ONE-HALF YEARS OLD WITH CONGENITAL MALFORMATION OF HYPOTHALAMUS BUT WITHOUT ADENOMA OF THE HYPOPHYSIS. J. M. CANTER VISSCHER-JOLLES and CORNELIA DE LANGE, Ann. pædiat. **163**:57 (Aug.-Sept.) 1944.

The case history is reported of a boy who was healthy up to the age of 2½ years but in whom Cushing's syndrome then developed with the exception of osteoporosis. He died at the age of 3½ years. Only a partial necropsy was permitted, but the testes, the brain and the hypophysis could be examined. The testes and the hypophysis proved normal save for a restricted number of cells showing hyaline changes. Macroscopically the brain was also normal, but there was a congenital deformity of the regio tuberoinfundibularis. By far the larger part of the tuber cinereum consisted of neuroglia without ganglion cells. The form of the infundibulum had greatly altered, and with it the form of the paraventricular nuclei. The writers lay stress on the necessity, first, to examine the brain and hypophysis even in cases in which no anomalies appear to the naked eye and, second, to examine in serial sections the hypothalamus, if the hypophysis appears normal. Cushing's syndrome may be caused by a basophilic adenoma of the hypophysis, but also by a process in the hypothalamus.

The interrelation between hypothalamus and hypophysis in these cases is difficult to understand.

AUTHORS' SUMMARY.

DIABETES INSIPIDUS WITH HYPOPHYSEAL NANISM AND SEVERE RENAL CALCULOSIS: REPORT OF A CASE. A. BIEBER, Riv. di clin. pediat. **44**:27, 1946.

A case of diabetes insipidus and dwarfism with clinical aspects of faulty phosphorus-calcium metabolism, of which renal calculosis is the most important symptom, is illustrated. It is thought that this may be due to a simultaneous lesion of the anterior hypophysis and of the diencephalic centers of water metabolism. This syndrome is complicated by hypercalcemia, a level of calcium in the urine, phosphaturia, hyperphosphoremia, renal calculosis and slight osteoporosis. The pathogenesis of this change in the mineral metabolism is discussed, without exclusion of the possibility that it may be due to hyperparathyroidism. The possibility of alterations in the functioning of the supposed diencephalic centers governing the phosphorus-calcium metabolism is suggested, joining in one pathogenetic mechanism the diencephalic-hypophysis syndrome and the alteration in the phosphorus-calcium metabolism.

AUTHOR'S SUMMARY.

Diseases of the Muscles, Bones, Joints and Lymph Glands

RICKETS AND INFANTILE SCURVY OCCURRING IN A CASE OF OSTEOGENESIS IMPERFECTA. RALPH S. BROMER, Am. J. Roentgenol. **55**:30 (Jan.) 1946.

Multiple etiologic agents may affect the skeleton simultaneously. Rickets and infantile scurvy, congenital syphilis and infantile scurvy, and rickets and lead poisoning are examples.

The author presents a case history of a patient with osteogenesis imperfecta who had rickets at 3 months of age and infantile scurvy at 21 months of age. The case presented roentgen changes indicative of osteogenesis imperfecta tarda rather

than those seen in the congenital type; however, the examination made when the patient was 3 months of age gave evidence that this condition had been present at birth.

HARRISON, Chicago.

OSTEOMYELITIS OF THE JAWS IN INFANCY. N. M. JACOBY and L. SAGORIN, Arch. Dis. Childhood **20**:166 (Dec.) 1945.

The treatment with penicillin of 2 infants with osteomyelitis of the maxilla and 1 with osteomyelitis of the mandible is described. The prognosis and the cosmetic result are dramatically improved and the duration of the disease greatly reduced.

KELLY, Milwaukee.

DYSTONIA MUSCULORUM PROGRESSIVA. CORNELIA DE LANGE, Ann. pædiat. **164**: 169 (April) 1945.

During life the diagnosis of dystonia musculorum progressiva was verified by competent neurologists. The illness began in the eighth year of the patient's life; death came when he was 46 years old.

The author made a microscopic investigation of the brain, the greater part of the spinal cord and the visceral organs. The striate body was practically normal, but in different parts the brain and the cord presented anomalies which doubtless proved their degenerative anlage. She thinks that in the cases of so-called idiopathic or degenerative dystonia there may be a disturbance in the function of the system of brain (spinal cord), nerves and muscles, perhaps depending on an abnormal metabolic process which escapes our present histologic technic.

AUTHOR'S SUMMARY.

HYPERACUTE STAPHYLOCOCCIC OSTEOMYELITIS: RECOVERY THROUGH IODINE AND SULFONAMIDE THERAPY. P. ROHMER, R. SACREZ and P. BEYER, Arch. franç. de pédiat. **3**:73, 1946.

This case concerned a girl of 18 months. A febrile attack was followed on the second day by an inflammatory edema involving the left arm and hand. The patient was apathetic and prostrated to the extent that examination was not painful. The joints were not attacked and lymph nodes throughout the area not palpable. Careful search revealed no sign of puncture wound. Examination showed tonsillar hypertrophy; the liver was slightly enlarged but the spleen was not felt. Hematologic examination was reported as follows: Leukocytes numbered 11,000, of which 70 per cent were polymorphonuclear cells, 24 per cent lymphocytes and 6 per cent monocytes. The urine showed only a trace of albumin.

Treatment consisted of a plaster cast and the administration of sulfathiazole, 3 Gm. the first and the second day and 2 Gm. on each of the following days. The temperature rose to 40 C. (104 F.), and the general condition showed only slight improvement. Pericarditis developed on the third day with characteristic signs of friction and changes shown on the roentgenogram. The blood culture was by this time positive for Staphylococcus aureus; fluctuation was noted on the lower and inner aspect of the arm. The child was semicomatose and extremely toxic. Transfusion of 25 cc. was ordered and sulfapyridine was substituted for sulfathiazole in doses of 3 Gm. daily. On the eighth day there was slight improvement and the temperature was 38 C. (100.4 F.), but prostration was still severe. On this day, puncture of the softened area was done, and 15 cc. of pus was withdrawn showing S. aureus in pure culture. Further transfusions were given both intravenously and intraperitoneally. On the ninth day there were convulsive seizures but the spinal fluid was normal; the blood picture was also satisfactory. Roentgenograms of the arm showed no osseous lesion. The following day iodine, 1.5 Gm. daily, was added to the sulfonamide therapy. From that time on, through a convalescence which continued for more than four hundred days during three readmissions, there was slow but definite improvement with complete recovery and without any

operative procedure. Iodine was given in the form of strong solution of iodine U. S. P. A total of 477 Gm. of sulfonamide drug and 187 Gm. of iodine was offered with apparent freedom from any damaging effect. AMESSE, Denver.

OSSEOUS LESIONS IN VON RECKLINGHAUSEN'S DISEASE. LORENZO EXPOSITO, Bol. Soc. cubana de pediat. **17**:266 (July) 1945.

The author discusses von Recklinghausen's disease generally with emphasis on the lesions of the bone under three headings: (*a*) osseous dystrophy (scoliosis, facial asymmetry, prognathism, and so forth); (*b*) dystrophic lesions with osteomalacia (rare, but of grave prognostic significance), and (*c*) localized osseous lesions (associated with a neurofibroma, a plexiform neuroma or dermatolysis). Two cases with lesions of the cranial bone are reported. KEITH, Rochester, Minn.

Skin Diseases; Allergy

TREATMENT OF ICHTHYOSIS. HYMAN H. GORDON, Arch. Dermat. & Syph. **52**:178 (Sept.) 1945.

The author describes two successful methods of treatment for ichthyosis and presents reports of cases illustrating each method. The first method comprises the sweating treatment, consisting of daily baths in 3 per cent sodium chloride solution followed by 10 per cent sodium chloride in hydrous wool fat. The second method consists of the administration of vitamin A in high daily doses, up to 200,000 units, with bile salts and neostigmine. MCINTOSH, Iowa City.

BETA DIMETHYLAMINOETHYL BENZHYDRYL ETHER HYDROCHLORIDE (BENADRYL) IN TREATMENT OF URTICARIA. ARTHUR C. CURTIS and BETTY BRECHNER OWENS, Arch. Dermat. & Syph. **52**:239 (Oct.) 1945.

In the theory that urticaria is a histamine reaction the new antihistamine drug beta dimethyl aminoethyl benzhydral ether hydrochloride (Benadryl) was given a therapeutic trial in several patients who had chronic or recurring urticaria. Benadryl was found to be of distinct benefit in 14 of the 18 subjects. The drug was administered orally in doses of 50 mg. to 100 mg., and only infrequent minor toxic manifestations were noted. Benadryl is palliative only, since the urticarial lesions recur when the drug is discontinued. MCINTOSH, Iowa City.

PENICILLIN OINTMENT: STUDIES OF STABILITY RELATIVE TO POTENCY AND ON THE SENSITIVITY OF THE HUMAN SKIN TO PATCH TESTS WITH OINTMENT. RALPH B. COOMBER, Arch. Dermat. & Syph. **52**:246 (Oct.) 1945.

The author studied the stability of the potency of penicillin ointment and the degree of tolerance exhibited by the skin to penicillin in ointment form. He concluded that the ointment rapidly lost its effectiveness in inhibiting the growth of bacteria. If the ointment was kept at a refrigerator temperature of 15 C., its apparent activity extended over a period of five days. Penicillin in ointment form was found to be relatively nonirritating to the skin. MCINTOSH, Iowa City.

QUANTITATIVE ESTIMATION OF THE ABSORPTION OF AN INGESTED ALLERGEN. JOSEPH R. SPIES, DORRIS C. CHAMBERS, HARRY S. BERNTON and HENRY STEVENS, J. Allergy **16**:267 (Nov.) 1945.

A method is described for the estimation of the quantities of allergen absorbed from the gastrointestinal tract when CS-1A (an allergenic polysaccharidic protein fraction) and defatted cottonseed are ingested.

"The method described may be applicable to the determination of an allergen in two substances by comparing the quantities of ingested substances required to induce equivalent effects in passively sensitized sites.

"By this method it was estimated that CS-1A contains a concentration of allergen approximately twenty-five times as great as defatted cottonseed."

HOYER, Cincinnati.

A QUANTITATIVE STUDY OF THE RELATION OF SYNTHETIC 3-PENTADECYL CATECHOL TO HYPERSENSITIVENESS TO RHUS TOXICODENDRON (POISON IVY) AS SHOWN BY THE PATCH TEST. HARRY KEIL, DAVID WASSERMAN and CHARLES R. DAWSON, J. Allergy **16**:275 (Nov.) 1945.

Synthetic 3-pentadecyl catechol is the saturated analogue of the active ingredient causing poison ivy dermatitis. Sixty-two persons sensitive to the poison ivy plant were sensitive to 3-pentadecyl catechol in concentrations of 1 per cent or less. Twenty-one persons were sensitive to 0.1 per cent concentration in acetone. For final evaluation a period of ninety-six hours of observation is requisite. In a few instances in which the reaction was negative with a 0.1 per cent solution, a positive reaction was obtained with a 1 per cent solution. The authors feel that this synthetic may be used for testing the skin for sensitivity to Rhus toxicodendron and related plants.

HOYER, Cincinnati.

ERYTHEMA EXSUDATIVUM MULTIFORME (HEBRA): BULLOUS TYPE. MARY W. CRITZ FLETCHER and RUTH C. HARRIS, J. Pediat. **27**:465 (Nov.) 1945.

Erythema multiforme bullosum, an unusual form of erythema exsudativum multiforme (Hebra), has been recognized for over one hundred years, but it is not commonly seen in hospitals or private practice. It is an acute inflammatory disease of the skin and the mucous membranes characterized by red to reddish purple macules, papules, vesicles, tubercles or lesions of the iris. Less commonly purpura, bullae, urticaria or angioneurotic edema is seen. This is accompanied by mild to severe constitutional symptoms, occasionally causing death. There is no known cause, but allergic reactions to food, drugs or bacteria are commonly considered as producing the disease.

Of 71,901 patients admitted to Willard Parker Hospital, the contagious disease hospital of Manhattan, 28 persons with erythema multiforme bullosum were found. Sixteen of those cases are reported here. In all cases the following characteristic lesions were seen: (1) multiform erythematous cutaneous lesions, (2) bullous formations on the skin or the mucous membranes and (3) presence of constitutional symptoms compatible with an acute infectious disease.

In this group of 16 cases there were 3 deaths. Over one half of the patients were under 10 years of age, and 10 of the patients were male. There was no outstanding seasonal, racial or geographic distribution. Etiologic factors were suggestive in 6 of the cases. In 3 cases the illness followed the use of sulfonamide compounds, gentian violet medicinal or solution of potassium arsenite. In 2 cases the disease occurred ten days after vaccinations for smallpox, and in 5 cases there was evidence of bacterial infections.

Constitutional symptoms included fever, sore throat, headache, vomiting, malaise and anorexia. There were symptoms referable to the eyes, the gastrointestinal, the respiratory and the genitourinary tract when those organs were involved. Seriously ill patients had chills, delirium, convulsions and coma.

The principal cutaneous lesions were pink to dark red macules and maculopapules, 14 of the patients presenting vesicles and large bullae. To a less extent generalized erythema, pustules, purpura, iritis, crusted lesions and desquamation occurred. Almost all the patients had a residual pigmentation. Lesions of the mucous membranes were commonly found in the mouth, the pharynx, the nose,

the vulva, the penis, the ears, the rectum and the vagina. Seven of the patients had a purulent conjunctivitis.

The illnesses lasted on an average of two to three weeks. The 3 deaths occurred within the first week. One autopsy was performed and the microscopic appearance of the cutaneous lesions was essentially as decided by Gans, McCarthy and Edgar.

Laboratory data obtained were not helpful in making the diagnosis. There was frequent evidence of concurrent respiratory and secondary cutaneous infections. Treatment was directed toward general support and combating the infections, the sulfonamide compounds and penicillin being used in these last few years.

One of the most striking facts to come out of this study was the difficulty in differential diagnosis. Only 1 patient was sent into the hospital with the correct diagnosis. Most frequently confused with this disease were diphtheria, chickenpox and vaccinia, their lesions of the skin and the mucous membranes and their constitutional symptoms being sometimes rather similar. Other incorrect diagnoses were smallpox, scarlet fever, measles, meningitis and impetigo. Undoubtedly familiarity with the syndrome of erythema multiforme bullosum would lead to more correct diagnoses.

AUTHORS' ABSTRACT.

THE DESTRUCTION BY TYROSINASE OF THE IRRITANT PRINCIPLES OF POISON IVY AND RELATED TOXICANTS. IRWIN W. SIZER and CLEMENS E. PROKESCH, J. Pharmacol. & Exper. Therap. **84**:363 (Aug.) 1945.

The authors recently suggested in a previously published paper that mushroom tyrosinase can inactivate extracts of poison ivy in vitro. They conclude from their interesting work that accompanying the oxidation of these toxic materials by tyrosinase there is an appreciable decrease in the dermatitis-producing properties as measured by using cutaneous patch tests on both human beings and guinea pigs. Tyrosinase is effective in the inactivation of the toxicants not only in vitro but also when applied to the human skin simultaneously with the toxicants or a few hours after they have penetrated into the skin. The use of tyrosinase in the treatment of poison ivy dermatitis in its early stages is suggested, although no information is as yet available concerning the utilization of this enzyme for the inactivation of the toxicants in the more advanced stages of the dermatitis.

PILCHER, Cleveland.

EFFECT OF RADON-CONTAINING OINTMENT ON CUTANEOUS LYMPH FLOW AND MINUTE VESSELS OF SKIN. J. Q. GRIFFITH JR., E. P. PENDERGRASS, C. R. PERRYMAN and J. HOOKER, Proc. Soc. Exper. Biol. & Med. **61**:70 (Jan.) 1946.

Human beings as well as dogs were used to study the effect of cutaneous application of radon-containing ointment (500 electrostatic units per milliliter, applied in a film 1 mm. thick, covered with oiled silk and left in place four hours) on hyperemia, lymphatic absorption and capillary permeability. Hyperemia was studied in the antecubital area of the forearm under a capillary microscope, and there was noted an increase of 100 per cent in capillary loops. Also, study of the dorsum of the foot of 6 rats revealed increase in flow of cutaneous vessels after application of radon ointment. Lymphatic flow was found to be increased following the application of radon as determined by the disappearance time of intracutaneously injected (0.04 cc.) patent blue in 8 normal men and 14 rats. Injection of 0.3 cc. of a 5 per cent solution of colloidal congo red dye in the jugular vein of 8 normal rats caused no difference in the color of the legs whether or not they were treated with radon. In 7 animals which had received roentgen irradiation to one leg one month previously the treated leg became red within five minutes. In addition, 4 men who had received many injections of penicillin resulting in local lymphedema with pain and swelling were relieved even strikingly in twelve hours after application of radon ointment.

HANSEN, Galveston, Texas.

Miscellaneous

CHILDREN'S IDIOSYNCRASIES. T. WOOD CLARKE, Arch. Pediat. **62**:498 (Nov.) 1945.

The author gives a general philosophic discussion of his concept of childhood idiosyncrasies, with rather detailed comments concerning the part played by various types of allergic reactions. The paper does not lend itself to further abstracting.

GRULEE JR., Minneapolis.

CHILDREN'S IDIOSYNCRASIES (CONCLUSION). T. WOOD CLARKE, Arch. Pediat. **62**:554 (Dec.) 1945.

The author discusses the manifold factors entering into feeding difficulties in the pediatric age group and states his opinion as to many of the offending elements and important considerations of a child's environment.

GRULEE JR., Minneapolis.

SUBCUTANEOUS ADMINISTRATION OF SODIUM SULFADIAZINE. KURT GLASER and GRACE LAWRENCE, J. Pediat. **27**:402 (Nov.) 1945.

Realizing the difficulties and shortcomings of the oral and intravenous administration of the sulfonamide compounds, the authors have studied and used the subcutaneous administration of sodium sulfadiazine and found its use satisfactory. Commercially supplied 10 cc. ampules of a 25 per cent solution of sodium sulfadiazine were used. The content was diluted with distilled water to make a 5 per cent solution. The dosage used, and recommended, was 1 grain per pound (132 mg. per kilogram) of body weight in twenty-four hours divided in two doses, given at twelve hour intervals.

The authors feel that several requirements have to be met before this method can be considered applicable: (1) absence of local irritation, (2) a concentration of the solution strong enough to make the total amount injectable at one time, (3) a high concentration in the blood and the maintenance of a high level in the blood and (4) clinical efficacy.

By means of four sample graphic charts, the authors prove that these requirements were met. A sufficient blood level was reached within one hour and the peak of concentration in the blood attained between two and three hours. The level was maintained sufficiently high for twelve hours, at the end of which time the next dose was due. The observation of the blood level curve during periods of restricted intake of water and periods of abundant intake showed the rapid elimination of sulfadiazine during the latter periods. The clinical response of the patients was excellent. No local or systemic toxic reactions were observed; however, it was felt that even in the event of irritative damage to the kidney, the oral, subcutaneous or intravenous administration of alkaline fluid would lower the blood level sufficiently fast to eliminate the drug from the body, as is evident in the graphs.

In conclusion, the authors state that the subcutaneous administration of a 5 per cent solution of sodium sulfadiazine is an advantageous and safe method of chemotherapy for use in hospitals as well as for the patient treated at home.

AUTHORS' ABSTRACT.

THE PERMEABILITY OF MYCOBACTERIA TO SULFONAMIDES AND SULFONAMIDE-LIKE AGENTS. DIRAN YEGIAN and VERA BUDD, J. Pharmacol. & Exper. Therap. **84**:318 (Aug.) 1945.

The sulfonamide compounds studied were the ones commonly used at present, and the organisms were Mycobacterium tuberculosis and Mycobacterium ranae. Washed cultures of the organisms were exposed to the drugs for some hours; they were then washed and the drug extracted. It was found that the sulfonamide

compounds entered the cells of the organisms. "The development of drug fastness does not appear to depend upon the change in permeability or binding of the sulfonamide to the bacterial cells."

PILCHER, Cleveland.

DISTRIBUTION AND FATE OF PENICILLIN IN THE BODY. WINDSOR C. CUTTING, F. P. LUDUENA, MARSHALL FIESE, HENRY W. ELLIOTT and JOHN FIELD II, J. Pharmacol. & Exper. Therap. **85**:36 (Sept.) 1945.

The study was made in rats and rabbits by subcutaneous (rat) and intravenous injection (rabbit). In both animals the liver, the heart and the striated muscle contained amounts of penicillin approaching the amount in the blood; the brain contained but a negligible quantity. The concentration in the bile (dogs) tended to exceed that in the blood, but this amount was insignificant in the total excretion of penicillin, as was the amount lost through the saliva. The major loss of penicillin continues to be in the urine. Renal obstruction greatly prolonged the excretion.

PILCHER, Cleveland.

UNIVERSITY MATERNITY HOSPITAL. RAUL BRIQUET, Matern. e inf. **1**:30 (June) 1945.

The author outlines the necessity for the establishment of a department of obstetrics and a maternity hospital in the new University of São Paulo. In addition to the need for hospital beds for obstetric cases there is great need for a hospital to take the lead in providing better care for the mothers and the newborn infants of Brazil.

CHRISTOPHERSON, San Diego, Calif.

PHARMACOLOGIC INVESTIGATIONS ON SULFATHIAZOLE AND SULFAMETHYLDIAZINE COMPARED WITH SULFAPYRIDINE, WITH SOME CLINICAL EXPERIENCES. H. VERHAGEN, Nederl. tijdschr. v. geneesk. **86**:3048 (Dec. 5) 1942.

A comparative study was made of sulfapyridine, sulfamethylthiazole and sulfamethyldiazine. This last-mentioned compound proved to be of great value, as much higher concentrations in the blood could be obtained, the excretion in the urine was much greater, and the toxic symptoms were less numerous than after use of the other compounds. Sulfamethylthiazole gave the lowest concentrations in the blood and was decidedly less toxic than sulfapyridine. Several complementary researches are mentioned, dealing with the distribution of the examined compounds in the plasma, the erythrocytes and several organs, and some researches on the diazo reactions in the urine. A few clinical observations give a less favorable impression of sulfamethylthiazole, while the good results obtained with sulfamethyldiazine justify the use of this drug.

VAN CREVELD, Amsterdam, Netherlands.

News and Comment

GENERAL NEWS

Fund for Investigations Having Therapeutic Interest.—The Committee on Therapeutic Research of the Council on Pharmacy and Chemistry has a fund made available by the American Medical Association to be expended in the promotion of investigations that have therapeutic interest. Applications for grants in this general field, which is conceived very broadly, are invited. An adequate description of the research proposed should be incorporated in the application. As the grants from the Council may well be small in relation to the total cost of investigations aided, information is requested as to whether the proposed research is a continuation of investigation which has been previously supported by some research fund and as to whether the work is to be supported in part by a grant or grants from other sources.

Applications should be in the hands of the Secretary of the Council, 535 North Dearborn Street, Chicago 10, Illinois, by June 1. To expedite transmission to members of the Committee, it is requested that six copies (five carbon copies) of each application be sent.

NOTICE

Application Fee for the American Board of Pediatrics, Inc.—Because of the increased cost of running the American Board of Pediatrics, Inc., the Board has found it necessary to raise the application fee to $125, effective May 1, 1947.

Book Reviews

Voluntary Health Agencies: An Interpretive Study. By Selskar M. Gunn and Philip S. Platt. Foreword by Louis I. Dublin. Price, $3.00. Pp. 364 plus 18, Index. New York: The Ronald Press Co., 1945.

There are over 20,000 voluntary health agencies in the United States, with at least 300,000 rather exceptional citizens serving on boards or committees of these agencies. The number of volunteer workers giving some of their time and effort outside board meetings would exceed a million, and this does not include the millions of Red Cross workers. Exclusive of that spent by the Red Cross, the money spent annually throughout the country approaches $50,000,000. It is obvious, therefore, that a critical evaluation of the purpose, function and prospects of these voluntary health agencies is of great importance to the future growth of organized health work in this country. The present study was launched under the auspices of the National Health Council in 1941 aided by a fund from the Rockefeller Foundation. The volume is well worth reading by pediatricians, many of whom are, no doubt, on the boards of these voluntary agencies; some, in fact, represent the medical leadership in their communities responsible for the initiation of the agencies. A voluntary health agency is defined as an organization administered by an autonomous board, which holds meetings, raises funds from private sources and spends money with or without paid workers, conducting a program directed primarily toward furthering public health by providing health services or health education or by advancing research or legislation related to health or by a combination of these activities.

One of the principal conclusions is that, in spite of voluntary health agencies having opened up new fronts in the attack on preventable diseases and in spite of their rapid growth, it is alleged, they have lagged behind the times. The report says: "They attempted to distribute the benefits of specialization without regard for the indispensable coordination. They have left many gaps of unmet needs and their diversity and overlapping of services and of appeals have confused the public. They have been slow in correcting the imbalance between the importance of health problems and the means to attack them. Under professional guidance they have adopted modern medical techniques with reasonable promptness but they have usually been noticeably slow in giving up established programs. . . . The agencies have generally tended to lag in their attitudes and practices in relation to social, economic and cultural changes as illustrated in their tardy adoption of community planning, of modern personnel policies, in their reliance upon doctrinaire educational methods and in their attitudes toward the growing importance of organized labor." This constitutes an indictment which seems to encompass both realities and exaggerations.

Among the recommendations to correct these supposed conditions, the following seem especially significant. Each voluntary agency should (1) regard its program as fluid and subject to change, being prepared not only to modify those activities that it carries on and to take on new ones but also to abandon or transfer some of its functions to other agencies, especially the official ones, and (2) cooperate actively with the official health agencies, with the professional and educational groups and with one another for advancing the common purposes.

The report comes out strongly for the development of community health councils and also recommends that boards of agencies should engage earnestly in self analysis and invite appraisal by competent outside authorities. It urges the selection of executives of the voluntary agency with exceeding care and the development of new wage and personnel policies in keeping with best modern practices in public service and in noncompetitive technical and professional activities of business enterprises.

There is an important chapter on financing voluntary health work. The authors are critical of the present approach. They decry the competition by agencies for the public's money. A few agencies with especially effective money-raising devices gain a disproportionate amount of the public's money for their programs, which tend to be narrow in interest and service. The unique and valuable experience obtained through the National War Fund is reviewed, and a similar unified appeal by voluntary health agencies is proposed. It is urged that the National Tuberculosis Association and the National Foundation for Infantile Paralysis broaden their fields of interest and service. The report goes on to state: "The wisest minds should determine the reasonable needs the voluntary agencies can most usefully serve, as teammates of the official agencies and in cooperation with one another, and the cost of their doing so practically, both on an immediate program and on an adjusted scale in the years ahead."

Pediatricians will find the report inadequate in its treatment of voluntary organizations in maternal and child health, although it does discuss the New York Maternity Center Association and the defunct American Child Health Association. Since the liquidation of the American Child Health Association represents the rare example of an agency dissolving after having fulfilled a useful, important function, the circumstances associated with its disappearance might have been examined with special care. On the other hand, if need and leadership are two of the criteria for establishing and maintaining a voluntary health agency, then there would seem to be need even today for a voluntary national child health agency.

The problem of voluntary health agencies in their relations with one another and with public agencies is not unlike the problem facing nations today in respect to international cooperation. The same questions of sovereignty, objectives, spheres of influence and personalities are involved. To the observer it would seem that closer working relationships among the voluntary agencies are a necessity. The length to which these working relationships will go, whether they stop at a loose federation or a strong union or somewhere in between, depends in the main on quality of leadership within the agencies and within the National Health Council, which sponsored the study and which now faces the challenge of securing sufficient funds and the driving person for putting into practice its recommendations.

Pediatricians will find this book a liberal education on the subject of organized action in health work. Since future progess will depend more and more on type of enterprise, the pediatrician should be familiar with its contents.

Human Embryology. By Bradley M. Patten, Ph.D., Professor of Anatomy in the University of Michigan Medical School. Price, $6. Pp. 776, with 1,336 illustrations. Philadelphia: The Blakiston Company (Division of Doubleday, Doran and Company, Inc.), 1946.

To dispel the possible impression that the reviewer has been too critical when reading this book, he will say at the outset that Professor Patten is to be congratulated highly for his excellent achievement. He has fulfilled admirably his endeavor to narrate in simple and readable form the phases of human embryology which are of special interest to medical students and physicians. The reader is impressed with the style of the text and the freshness of its approach. The developmental processes are presented as a story of dynamic events, and emphasis is placed on the functional significance as they unfold in sequence. The topics are well organized and clearly set forth. He has been skilful and especially successful in the way in which he has correlated human embryologic and adult structures and has portrayed the basis for the explanation of developmental anomalies. Special thought has been given to expounding those aspects of human embryology which constitute much of the background of other branches of medical science, particularly obstetrics and gynecology, pediatrics and surgery.

The subject matter is divided into nineteen chapters, although the headings are not labeled as chapters, and is taken up under the following titles: (1) introduction; (2) reproductive organs, gametogenesis; (3) sexual cycle and fertilization; (4)

cleavage, germ layers and establishment of embryonic body; (5) early differentiation of the body and establishing of organic systems; (6) fetal membranes and placenta; (7) age, growth and changes in external form of body; (8) twins, double monsters and teratology; (9) integumentary system; (10) connective tissues and skeletal system; (11) the muscular system; (12) development of the nervous system; (13) the sense organs; (14) development of the face and jaws and the teeth; (15) development of the digestive and respiratory systems; (16) body cavities and mesenteries; (17) ductless glands and pharyngeal derivatives; (18) development of the urogenital system, and (19) development of the circulatory system. In reading over these titles one is struck by their inconsistency; why use the phrase "development of" in some chapter headings on organogeny and not in others? Though the arrangement of the subject matter is good for the most part, in other respects its logic is not clear: Why place the circulatory system at the end of the book, when this system is the first to function in the embryo?

Because it is impossible obviously, in a brief review, to evaluate every chapter fairly, only a few points will be singled out at random for criticism. Any student who is looking for a concise survey of the history of embryology will find the first or introductory chapter wholly inadequate. But on reading this chapter he will have no reason to doubt the value of the subject of embryology in the medical curriculum or be skeptical of its methods employed in the laboratory.

Referring to chapter 4, which carries the story of development to the end of the first two weeks, one can approve the omission of most of the comparative and theoretic material in Patten's textbook, if his assumption is correct that the student during his premedical training has become familiar with the processes of cleavage and formation of germ layers in vertebrate animals below mammals. What is more disturbing is that before the printing of the book Patten did not revise this chapter and bring it up to date by including the youngest implanted human embryos known, namely the 7½ day and 9½ day specimens described and figured by Hertig and Rock in 1942. In view of these specimens, Patten's statement that after the three or four day journey through the oviduct the conceptus remains free in the uterine cavity for five or six days, before it becomes implanted in the endometrium, can be challenged.

Chapter 5 represents one of the best chapters of the book, for the exposition correlates the early changes in the external form of the embryonic body with those of its internal configuration. Most other embryologic textbooks have failed to provide this point of view. Unfortunately, Patten makes extensive use of sections of pig embryos, when he could have figured those of human embryos to far better advantage instead. Patten's argument for a compromise between textbook and laboratory manual by including the student's available laboratory material as the basis of his descriptions does not hold, for such inclusion in the textbook is fragmentary at best. With the help of the laboratory instructor, the student, referring to portrayed sections from human embryos, would find his way through the corresponding stages of pig embryos quite as readily as the other way around. Despite this difference of opinion, the reviewer compliments Patten for having produced this admirable chapter by introducing the description of the establishment of the organ systems. In it he has carried along the study of the organ systems until the embryo has reached the age of about 6 weeks. In subsequent chapters the story of development of each organ system is picked up separately and followed to its conclusion.

The functional correlations have been emphasized particularly in dealing with the nervous and the circulatory system, the one as coordinator and the other as purveyor in their intimate interrelations with all other systems of the body. Though this is the proper approach, it must not be allowed to overshadow the main course of the embryologic story. In a number of places throughout the book, adult physiology crowds out certain significant details of development which might well be included. As an instance of this is found in chapter 13 in which the functions of the scala tympani and the scala vestibuli are introduced but the differentiation of the perilymphatic spaces is left to a few ineffective figures. No mention is made of the regressive changes which play a part in their formation.

Rarely is there a textbook in which all chapters are of equal excellence. In Patten's book the reviewer regards the discussion of the development of the metanephros, for example, as not satisfactory, and that pertaining to the lymphatic system as rather disappointing.

On the whole the text is easily read and in some places is entertaining because of the mechanism involved in the cessation of invasion of the trophoblast in the uterine mucosa. The author says, "Some investigators see in the phenomenon a nicely balanced cooperation between fetal and maternal tissues, whereas others—probably a matter of bellicose temperament—see the trophoblastic growth as an invasion, and interpret its checking as the result of a counterattack on the part of the maternal tissues."

It being one of the purposes of Patten's textbook to emphasize those phases of embryology which would be helpful in understanding the plan of the body as it is seen in human gross anatomy, he should have been more careful in his use of the terms of "anterior" and "posterior" instead of "cranial" and "caudal." When the medical student is told that "anterior" is synonymous with "ventral," and "posterior" with "dorsal," such phrases as "anterior kidney" (pronephros), "posterior kidney" (metanephros), "posterior to level of heart," and "extreme posterior portion of body cavity" are definitely misleading or confusing.

Since the bibliography which Patten gives at the end of his book (pages 698 to 740) is broken down in chapters, it would be much more effective at the end of each chapter, and less time would be spent in finding the references.

Even though the book is voluminous, there are not many typographic errors. But occasionally the misspelling of foreign names upsets one's composure, as for instance, when one reads "Mollendorf" instead of "Möllendorff" and "Sicker" instead of "Sicher."

The outstanding trait of Patten's book is its lavish use of pictures, which may be said to compose its backbone. There are 1,366 drawings and photographs, 53 of which are in color. A great number of the figures are original, drawn by the author or under his supervision. Many of them are unique and especially instructive (e. g., fig. 106). The portrayal of successive developmental stages on the same page or plate is a feature of inestimable value to the student in his endeavor to grasp the sequence of morphogenetic or histogenetic events. But in many cases such grouping with its complete labeling makes the pages so crowded that the clarity of the individual figures becomes lost in the maze and the attention of the eye is diverted. Furthermore, the lack of uniformity or consistency in the character of the labeling of the figures may be only a minor defect, yet detracts from the appearance of the pages, especially when seen side by side. There are some irrelevant illustrations. Relative to the colored illustrations, it can be said that in some cases (e. g., fig. 92) the choice of color is of no value, and in others its use (e. g., in fig. 148) would enhance their effectiveness. In some of the colored pictures, the colors are "dirty" and not "contrasty" enough, hence add little illustrative value.

Some students would prefer more tables and not such complicated diagrams, as represented by figures 40 and 194, for example. The latter figure of the functional plan of the nervous system would require considerable time even for the neurologist to unravel, to say nothing of the beginner. Indeed, some of the figures contain more neurology than the student of embryology can handle effectively.

The index of the book is notable in that the illustrations on the pages cited are referred to in numbers set in bold face type.

Finally, the Blakiston Company is to be commended highly for having met so fully the exacting demands of Professor Patten for the creation of a book of superior quality. The book is precise in its printing and bound attractively and serviceably.

Pneumoperitoneum Treatment. By Andrew Ladislaus Banyai, M.D. Price, $6.50. Pp. 376, with 74 illustrations. St. Louis: C. V. Mosby Company, 1946.

This volume thoroughly discusses a form of therapy which is not often used by the practicing clinician. The book opens with excellent chapters on the history

and technic of pneumoperitoneum. Special chapters are alloted to the complications of this procedure before the clinical applications are presented. The major portion of the text deals with tuberculosis of the peritoneum, the digestive tube and the lungs. The chapter on tuberculous enterocolitis devotes a number of pages to clinical symptoms and laboratory and roentgenologic diagnosis, which the reviewer feels is unnecessary in a volume primarily dedicated to a therapeutic procedure. The inclusion of 44 reports of cases in this chapter does not add to the value of the text. One hundred and twenty-nine pages are devoted to the treatment of pulmonary tuberculosis. The physiologic aspects of pneumoperitoneum on the apicobasal diameter, the volume and the surface of the lung are discussed. The author wisely emphasizes that pneumoperitoneum is to be used only when pneumothorax is contraindicated or has failed. In cases in which interruption of the phrenic nerve is desirable, pneumoperitoneum is advocated as an associated procedure in order to elevate further the domes of the diaphragm. Throughout the discussion, emphasis is carefully placed on proper selection of patients on whom pneumoperitoneum may be done.

Several chapters discuss miscellaneous application of pneumoperitoneum. The reviewer does not feel that adequate evidence is presented to indicate that pneumoperitoneum is of value in treating pulmonary abscess, bronchial asthma, bronchiectasis and pulmonary emphysema.

The format is excellent, and many reproductions of roentgenograms are included in the volume. Throughout the book the opinions of other workers interested in this form of therapy are presented. This gives the reader a complete survey of the subject but makes reading somewhat difficult. A detailed bibliography and an index have been excellently compiled.

The Child From Five to Ten. By Arnold Gesell, M.D., and Frances L. Ilg, M.D., in collaboration with Louise Bates Ames, Ph.D., and Glenna E. Bullis. Price $4. Pp. 475, with illustrations. New York: Harper & Brothers, 1946.

Dr Gesell and Dr. Ilg, with their collaborators, have written a monograph on the development of children from 5 to 10 years of age, which carries on their work with younger children into the school years. It therefore extends their observations on the development of children through half of the span of growth.

Part 1 is concerned with the picture of the entire cycle of development with emphasis on mental growth and the effect of environment on it, particularly that of parents and teachers.

Part 2 gives first a series of cross sectional studies of children from 4 weeks to 4 years of age. This is followed by studies of each of the years from 5 to 10. In each chapter the authors describe their behavior "profile" of the child, followed by a picture of individual traits at each age listed under ten headings: motor characteristics, personal hygiene, emotional expression, fears and dreams, self and sex, interpersonal relations, play and pastimes, school life, ethical sense and philosophic outlook.

After this presentation, the authors undertake, in the third part, to give a longitudinal portrayal of each of these traits throughout the 5 to 10 year age period.

The volume is beautifully printed and illustrated, which makes it easily readable. However, it is not designed for mere reading. It is a source book for information about children of the early school period, which will be studied and referred to by pediatricians, parents, nurses and teachers for many years to come.

This reviewer feels completely inadequate to express an opinion as to the validity of the various behavior "profiles" or of the gradients of developing traits, and suspects that this will be the feeling of almost any pediatrician who reads the book. It might be contended that the source of the observations on which it is based, 50 children of high average or superior intelligence, is not adequate material from which to draw any general conclusions as to trend in human growth, and the critically minded physician might ask for more of the direct observations made on the children as a means of evaluating the conclusions drawn.

Nevertheless, bearing in mind the meticulous care with which the authors have collected and reported their previous data on growth and development, one feels that this comprehensive statement of growth in the early school period should be gratefully received. The authors have given us "something to shoot at." It is to their great credit that they have attempted this monumental project, a task which seems almost impossible. Certainly the book merits a place in the library of any one interested in child growth or behavior.

The Health of the School Child. By Gertrude E. Cromwell, R.N., M.S. Price, $2.50. Pp. 256, with 46 illustrations. Philadelphia: W. B. Saunders Company, 1946.

While this book is planned for nurses, it should be of interest to pediatricians because of the large part played by nurses in school health services. It not only gives a good interpretation of what a school health program is and the principles involved but offers valuable suggestions to the school nurse.

It stresses the philosophy that "the schools can do a better job in health education than they are now doing, but if they are to do this work well, it will have to be as health education and child protection and not by actually supplying health services which the community should provide." With this point of view the whole program is considered to indicate how the nurse functions, the problems she faces and her relation to the responsibilities of teachers, principals, parents, physicians and many others who serve children. Appropriate emphasis is given to using the findings of the school medical appraisal, to live records and to the selection of special children who seem to be most in need of medical guidance.

The problem of the school physician's recommendation and the possibility that the private practitioner may have a different opinion is recognized as placing a difficult decision on the nurse. However, it is properly pointed out that the school physician "need not make a definite statement to the parent of the existence of a defect nor need he make a specific recommendation for the type of correction, . . ." but nevertheless, "if the school physician hopes to see the parent do anything about his recommendations, his recommendations must be made in such a way that the parent approaches the family physician with a reasonable certainty that the child really needs medical care." She mentions that the school physician might make a personal contact with the family physician, but the importance of avoiding two medical opinions is not given the emphasis that this reviewer regards as essential. However it is a medical problem, and nurses should, as stated, "use constant care in the type of statements made to parents and children if they wish to avoid many of these misunderstandings with the medical profession."

It is significant that this up-to-date book for nurses discusses this neglected problem because both school physicians and practitioners have too often failed to accept any responsibility for a proper exchange of opinion. To make such a public service function effectively, no doubt, the school physician must take the initiative in interpreting the basis for his opinion regarding the needs of the child.

Directory of Pediatric Societies *

INTERNATIONAL

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Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto 2
Secretary: Dr. S. G. Ross, 1390 Sherbrooke St. W., Montreal.
Place: New York. Time: July 14-17, 1947.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

Pan American Congress of Pediatrics

President: Dr. Felix Hurtado, Habana, Cuba.
Place: Mayflower Hotel, Washington, D. C. Time: July 9-12, 1947.

Save the Children International Union

President: Mrs. Gordon Morier.
Secretary: Dr. Georges Thélin, 43 Quai Wilson, Geneva, Switzerland.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

Associação Paulista de Medicina, Secçaõ de Pediatrias

President: Dr. Vicente Lara.
First Secretary: Dr. Armando de Arruda Sampaio.
Second Secretary: Dr. Luiz Augusto Monteiro Toledo, Av. Brigadeiro Luiz Antonio 393, 1° Andar, São Paulo, Brazil.
Time: Twelfth of every month, 8:30 p. m.

British Paediatric Association

President: Prof. G. B. Fleming, 13 Lynedoch Crescent, Glasgow.
Joint Secretary: Prof. Alan Moncrieff, Hospital for Sick Children, Great Ormond St., London, W. 1.

Danish Pediatric Society

President: Dr. E. Lenstrup, Copenhagen.
Secretary: Dr. Gjørup, Dronning Louises Børnehospital, Copenhagen.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

NEDERLANDISCHE VEREENIGING VOOR KINDERGENEESKUNDE

President: Dr. J. L. Keyzer, 114 St. Josephstr., Tilburg.
Secretary: Dr. H. Reerink, 2B Paul Krugerstr., Arnheim.
Place: Children's Hospital or Pediatric Clinic. Time: Three times a year.

PALESTINE JEWISH MEDICAL ASSOCIATION, SECTION OF PHYSICIANS OF CHILDREN'S DISEASES

President: Prof. L. F. Meyer, 29 Toelsohn St., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

ROYAL SOCIETY OF MEDICINE, SECTION FOR THE STUDY OF DISEASES IN CHILDREN

President: Prof. Norman Capon, 49A Rodney St., Liverpool, England.
Secretary: Dr. J. N. O'Reilly, 46 Harley St., London W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p. m.

SOCIEDAD BOLIVIANA DE PEDIATRIA

President: Dr. Ernesto Trigo Pizarro.
Secretary: Dr. Carlos Ferrufino, Casilla 272, La Paz, Bolivia.
Place: La Paz, Bolivia.

SOCIEDAD CUBANA DE PEDIATRIA

President: Dr. Teodosio Valledor, Habana.
Secretary: Dr. Carlos Hernandez Miyares, Hospital Nuestra Señora de las Mercedes L y 21, Apartado 2430, Habana.
Place: Cátedra de Clinica Infantil, Hospital Nuestra Señora de las Mercedes y Hospital Municipal de Infancia, Habana. Time: Last Wednesday of every month.

SOCIEDAD DOMINICANA DE PEDIATRIA

President: Dr. Alberto Peguero, Ciudad Trujillo, R.D.
Secretary-Treasurer: Dr. Jaime Jorge, Ciudad Trujillo, R.D.
Place: Children's Ramfis Hospital. Time: 8 p. m., last Thursday of every month.

SOCIEDAD ECUADORIANA DE PEDIATRIA

President: Dr. Francisco de Icaza Bustamente.
Secretary: Dr. M. I. Gómez Lince, P. O. Box 693, Guayaquil.

SOCIEDAD MEXICANA DE PEDIATRIA

President: Dr. Luis Berlanga Berumen, Bucareli No. 85, Altos, Mexico.
Secretary: Dr. Jésus Alvarez de los Cobos, Ignacio Mariscal 124, Mexico.

SOCIEDAD DE PEDIATRÍA DE CÓRDOBA

President: Dr. Juan Francisco Herrera, Córdoba, Argentina.
Secretary: Dr. Bernardo Serebrinsky, Dean Funes 2000, Esq. Ocaña (N.), Córdoba, Argentina.
Place: Comite pro Defenso del Niño, Dean Funes 2000, Córdoba, Argentina. Time: Once a month.

SOCIEDAD DE PEDIATRIA DEL LITORAL

President: Dr. Jose E. Celoria, Hospital Centenario, Rosario, Argentina.
Secretary: Dr. Gloria Lovell, Hospital Centenario, Rosario, Argentina.

SOCIEDAD DE PEDIATRÍA DE SANTIAGO DE CUBA

President: Dr. Antonio Béguez César, Sagarra 107, Santiago de Cuba.
Secretary: Dra. Susana Texdó Vaillant, Padre Pico 57, Santiago de Cuba.
Place: Colegio Médico. Time: Last Tuesday of every month.

Sociedad Venezolana de Puericultura y Pediatria

President: Dr. Pastor Oropeza, Caracas.
Secretary: Dr. Carlos E. Castillo, Hospital Municipal de Niños, Caracas.
Place: Hospital Municipal de Niños Jose Manuel de los Rios, Caracas.

Société de Pédiatrie de Paris

President: Dr. Leveuf, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Maladies, 149 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

Swedish Medical Society, Section for Pediatrics and School Hygiene

President: Prof. Arvid Wallgren, 53 Strandvägen, Stockholm.
Secretary: Dr. Henning Magnusson, 58 Odengatan, Stockholm.
Place: Various clinics and hospitals in Stockholm and Uppsala. Time: Second Friday of each month (except summer).

Uruguayan Society of Pediatrics

President: Dr. Jose Bonaba, Montevideo.
Secretary: Dr. Héctor Fossatti, Durazno 1882, Montevideo.
Place: Club Medico del Uruguay, Avenida Agraciado 1464 (Piso 13), Montevideo.

NATIONAL

American Medical Association, Scientific Assembly, Section on Pediatrics

Chairman: Dr. John Aikman, 184 Alexander St., Rochester, N. Y.
Secretary: Dr. Gilbert J. Levy, 188 S. Bellevue Blvd., Memphis, Tenn.

American Academy of Pediatrics

President: Dr. Jay I. Durand, 515 Cobb Bldg., Seattle, Wash.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.

American Hospital Association, Massachusetts Hospital Association

Chairman: Dr. Frank Wing, Boston.
Secretary: Dr. W. Franklin Wood, McLean Hospital, Waverly 79, Mass.

American Pediatric Society

President: Dr. Harold K. Faber, 2361 Clay St., San Francisco.
Secretary-Treasurer: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago 12.

Canadian Society for the Study of Diseases of Children

President: Dr. H. S. Little, 300 Dufferin Ave., London, Ontario.
Secretary-Treasurer: Dr. Elizabeth Chant Robertson, 67 College St., Toronto 2.

Society for Pediatric Research

President: Dr. Donovan J. McCune, 3975 Broadway, New York.
Secretary: Dr. Robert Ward, Bellevue Hospital, New York 16.

SECTIONAL

Intermountain Pediatric Society

President: Dr. Wesley H. Anderson, 2404 Washington Blvd., Ogden, Utah.
Secretary-Treasurer: Dr. F. M. Kriete, State Capitol, Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month. 8 p. m.

New England Pediatric Society

President: Dr. James Marvin Baty, 1101 Beacon St., Brookline, Mass.
Secretary-Treasurer: Dr. Charles D. May, 300 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Three meetings a year, occurring from September to May.

North Pacific Pediatric Society

President: Dr. Percy Guy, 502–2d Ave., Seattle, Wash.
Secretary: Dr. Aldis B. Johnson, 515 Cobb Bldg., Seattle, Wash.

Northwestern Pediatric Society

President: Dr. George Kimmel, Redwing, Minn.
Secretary-Treasurer: Dr. Northrop Beach, 1009 Nicollet Ave., Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

Rocky Mountain Pediatric Society

President: Dr. Jackson L. Sadler, 109 W. Olive St., Ft. Collins, Colo.
Secretary: Dr. Edwin T. Williams, 1850 Gilpin St., Denver 6.

Southern Medical Association, Section of Pediatrics

Chairman: Dr. Stewart H. Welch, 117 S. 20th St., Birmingham 5, Ala.
Secretary: Dr. W. Ambrose McGee, 1601 Monument Ave., Richmond 20, Va.

STATE

Alabama Pediatric Society

President: Dr. Jerome C. Chapman, 2160 Highland Ave., Birmingham.
Secretary-Treasurer: Dr. Ruth Berrey, 2021–6th Ave. N., Birmingham.

Arizona Pediatric Society

President: Dr. W. P. Sherrill, 342 W. McDowell Rd., Phoenix.
Secretary: Dr. W. F. Schoffman, 926 E. McDowell Rd., Phoenix.
Place: Phoenix or Tucson. Time: At time of state meeting.

Arkansas State Pediatric Association

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

California State Medical Society, Section on Pediatrics

Chairman: Dr. Charles W. Leach, 2000 Van Ness Ave., San Francisco 9.
Secretary: Dr. Chester I. Mead, 1930 Truxton Ave., Bakersfield.

Florida State Pediatric Society

President: Dr. James R. Boulware, Lakeland.
Secretary: Dr. Hugh A. Carithers, 2000 Park St., Jacksonville 4.
Place: Concurrent with state association convention and fall meeting.

Georgia Pediatric Society

President: Dr. Alton Johnson, 102 E. Central Ave., Valdosta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Place: Atlanta. Time: At time of annual state meeting.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. David Gaberman, 1179 Allyn St., Hartford, Conn.
Secretary: Dr. Herman Yannet, Southbury Training School, Southbury.

Illinois State Medical Society, Section on Pediatrics

Chairman: Dr. Gerard N. Krost, 2376 E. 71st St., Chicago.
Secretary: Dr. Frederick H. Maurer, 331 Fulton St., Peoria 2.

Indiana State Pediatric Society

President: Dr. K. T. Knode, 1105 E. Jefferson Bldg., South Bend.
Secretary-Treasurer: Dr. Matthew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

Iowa Pediatric Society

President: Dr. Arnold M. Smythe, 406–6th Ave., Des Moines.
Secretary-Treasurer: Dr. James Dunn, 414 Blackhawk Hotel, Davenport.

Louisiana State Pediatric Society

President: Dr. S. George Wolfe, 1560 Line Ave., Shreveport.
Secretary-Treasurer: Dr. W. C. Rivenbark, 1448 Louisiana Ave., New Orleans 15.

Medical Society of State of New York, Section on Pediatrics

Chairman: Dr. Carl H. Laws, 12 Pierrepont St., Brooklyn, N. Y.
Secretary: Dr. George R. Murphy, 292 Madison Ave., New York.

Medical Society of the State of Pennsylvania, Pediatric Section

Chairman: Dr. Joseph A. Gilmartin, 3700–5th Ave., Pittsburgh 13.
Secretary: Dr. Carl C. Fischer, 100 W. Coulter St., Philadelphia 44.

Michigan State Medical Society, Pediatric Section

Chairman: Dr. Donald J. Barnes, 3001 W. Grand Blvd., Detroit, Mich.
Secretary: Dr. Mark F. Osterlin, Central Michigan Children's Clinic, Traverse City.

Mississippi State Pediatric Society

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

Nebraska Pediatric Society

President: Dr. Paul N. Morrow, 1614 Medical Arts Bldg., Omaha 2.
Secretary-Treasurer: Dr. Michael Crofoot, 1407 Medical Arts Bldg., Omaha 2.
Place: As announced by committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

New Mexico State Pediatric Society

President: Dr. M. K. Wylder, 221 W. Central Ave., Albuquerque.
Secretary-Treasurer: Dr. Ly Werner, 221 W. Central Ave., Albuquerque.

North Carolina Pediatric Society

President: Dr. Charles R. Bugg, Professional Bldg., Raleigh.
Secretary: Dr. Charles F. Williams, 817 Hillsboro St., Raleigh.

Northern California Pediatric Society

President: Dr. Edith M. Meyers, 431–30th St., Oakland.
Secretary: Dr. A. L. Gleason, 411–29th St., Oakland 9.
Place: San Francisco. Time: Second Thursday of February, April, September and November.

Oklahoma State Pediatric Society

President: Dr. J. B. Snow, 625 N. W. 10th St., Oklahoma City.
Secretary: Dr. Bertha Levy, 1200 N. Walker St., Oklahoma City.
Place: With Oklahoma State Medical Association. Time: Annual Meeting.

South Carolina Pediatric Society

President: Dr. George D. Johnson, Spartanburg.
Secretary-Treasurer: Dr. B. O. Ravenel, Roper Hospital, Charleston.

Tennessee Pediatric Society

President: Dr. F. T. Mitchell, 376 S. Bellview, Memphis.
Secretary-Treasurer: Dr. W. O. Vaughan, 2103 Hayes St., Nashville 5.
Time: Second Monday in April.

Texas Pediatric Society

President: Dr. Max Woodward, 202 N. Travis St., Sherman.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmount Ave., Dallas 4.

Virginia Pediatric Society

President: Dr. Emily Gardner, 1100 W. Franklin St., Richmond 20.
Secretary: Dr. Louise Galvin, 214 S. Boulevard, Richmond 21.

West Virginia State Medical Society, Section on Pediatrics

President: Dr. Jack Basman, 1021 Quarrier St., Charleston.
Secretary: Dr. Harry E. Baldock, Medical Arts Bldg., Charleston.

LOCAL

Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. J. I. Hartman, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. Alexander N. Freed, 2012 W. 25th St., Cleveland.
Place: Cleveland Medical Library Bldg. Time: 8:15 p. m., October, December, February and April.

Academy of Medicine, Toronto, Section of Pediatrics

President: Dr. J. H. Ebbs, 13 Queen's Park, Toronto, Canada.
Secretary: Dr. J. F. McCreary, 170 St. George St., Toronto, Canada.
Place: Academy of Medicine. Time: 8:30 p. m., third Thursday of each month.

Baltimore City Medical Society, Pediatric Section

Chairman: Dr. Charles O'Donovan Jr., 5 E. Read St., Baltimore.
Secretary: Dr. T. Campbell Goodwin, 16 E. Biddle St., Baltimore.

Bronx Pediatric Society

President: Dr. Harry S. Pizer, 1726 Davidson Ave., New York.
Secretary: Dr. Nathan M. Greenstein, 1488 Metropolitan Ave., New York.
Place: Morrisania City Hospital. Time: 8:30 p. m., second Wednesday of each month, except June, July, August and September.

Brooklyn Academy of Pediatrics

President: Dr. George E. Brockway Jr., 176 Fenimore St., Brooklyn.
Secretary: Dr. Bernard Benjamin, 845 Park Pl., Brooklyn 16.
Place: Granada Hotel. Time: 8:45 p. m., fourth Wednesday of February, March, April, October and November.

Buffalo Pediatric Society

President: Dr. Douglas P. Arnold, 159 Bidwell Parkway, Buffalo, N. Y.
Secretary: Dr. Richard A. Downey, 786 Forest Ave., Buffalo 9, N. Y.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p. m., first Monday of each month from September to June.

Central New York Pediatric Club

President: Dr. Arthur W. Benson, 2 St. Paul St., Troy.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Places: Various cities in New York. Time: Third Tuesday of April and October.

Chicago Pediatric Society

President: Dr. H. William Elghammer, 2371 E. 71st St., Chicago.
Secretary: Dr. Alvah L. Newcomb, 723 Elm St., Winnetka, Ill.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May inclusive.

Cincinnati Pediatric Society

President: Dr. Leo S. Friedman, 666 Rockdale Ave., Cincinnati 29.
Secretary: Dr. George Renner, 3144 Jefferson Ave., Cincinnati.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

Dallas Pediatric Society

President: Dr. Shirley Hodges, 2703 Oak Lawn Ave., Dallas, Texas.
Secretary-Treasurer: Frances M. Love, 4585 Belfort, Dallas 4.
Place: Children's Medical Center. Time: 1 p. m., third Saturday and 8:30 p. m., the first Thursday of each month.

Detroit Pediatric Society

President: Dr. Otto Grob, 651 Fisher Bldg., Detroit 2, Mich.
Secretary: Dr. Harold B. Rothbart, 773 Fisher Bldg., Detroit 2, Mich.
Place: Variable. Time: Third Wednesday of each month.

Houston Pediatric Society

President: Dr. George Salmon, 1220 Bartlett St., Houston, Texas.
Secretary: Dr. Betty Moody, 526 Richmond Rd., Houston, Texas.
Place: River Oaks Country Club. Time: 7:30 p. m., last Tuesday of each month

Kansas City (Missouri) Pediatric Society

President: Dr. Harry M. Gilkey, 1624 Professional Bldg., Kansas City.
Secretary: Dr. Leland Speer, 1022 Parkway, Kansas City.
Place: Kansas City General Hospital. Time: On call.

Knoxville-Oak Ridge Pediatric Society

President: Dr. Henry S. Christian, 205 Medical Arts Bldg., Knoxville, Tenn.
Secretary: Dr. John Eggleston, Oak Ridge Hospital, Oak Ridge, Tenn.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Albert L. Hill, 1401 S. Hope St., Los Angeles.
Secretary-Treasurer: Dr. Robert Simonds, 1925 Wilshire Blvd., Los Angeles.
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Henry Rascoff, 895 Eastern Parkway, Brooklyn.
Secretary: Dr. Harold Levy, 750 St. Marks Ave., Brooklyn.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., fourth Monday of each month.

Medical Society of the County of Queens, Inc., Section on Pediatrics

Chairman: Dr. Meyeron Coe, 217-02-91st Ave., Queens Village, N. Y.
Secretary-Treasurer: Dr. Louis Appel, 143-42 Cherry Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. John Washington, 2203 Wyoming Ave., Washington, D. C.
Secretary-Treasurer: Dr. George Maksim, 1418 Good Hope Rd. S.E., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: 8 p. m., third Thursday of October, January, March and May.

Memphis Pediatric Society

President: Dr. Kinsey M. Buck, 1193 Madison Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. Barton Etter, 1024 Madison Ave., Memphis, Tenn.

Milwaukee Pediatric Society

President: Dr. G. H. Fellman, 231 W. Wisconsin Ave., Milwaukee.
Secretary-Treasurer: Dr. R. P. Showalter, 411 E. Mason St., Milwaukee 2.
Place: Milwaukee Children's Hospital. Time: Second Wednesday in February, April, June, October and December.

New York Academy of Medicine, Section of Pediatrics

Chairman: Dr. Robert O. Du Bois, 122 E. 76th St., New York.
Secretary: Dr. Harold W. Dargeon, 1095 Park Ave., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from November to May, inclusive, 8:30 p. m.

Oklahoma City Pediatric Society

President: Dr. J. B. Snow, 625½ N. W. 10th St., Oklahoma City.
Secretary: Dr. Bertha Levy, 1200 N. Walker St., Oklahoma City.
Place: Oklahoma Club. Time: Third Thursday of each month.

Philadelphia Pediatric Society

President: Dr. Arthur M. Dannenburg, 235 S. 15th St., Philadelphia 2.
Secretary: Dr. D. Stewart Polk, Rosemont, Pa.
Place: College of Physicians, 19 S. 22d St. Time: 8:30 p. m., second Tuesday from October to May, inclusive.

Pittsburgh Pediatric Society

President: Dr. Elwood Stitzel, 403 Central Trust Bldg., Altoona, Pa.
Secretary-Treasurer: Dr. C. J. Stoecklein, Medical Arts Bldg., Pittsburgh 13.
Place: Pittsburgh Academy of Medicine. Time: Second Friday in October, December, February and April.

Richmond Pediatric Society

President: Dr. Edwin L. Kendig Jr., 828 W. Franklin St., Richmond 20, Va.
Secretary-Treasurer: Dr. Thomas S. Chalkley, 1200 E. Broad St., Richmond, Va.
Place: Medical College Hospital. Time: 8 p. m., third Thursday of each month, except June, July and August.

Rochester Pediatric Society

President: Dr. William L. Bradford, 260 Crittenden Blvd., Rochester 7, N. Y.
Secretary-Treasurer: Dr. Donald D. Posson, 222 Chili Ave., Rochester 11, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee.
Time: Third Friday of each month from October to May.

St. Louis Pediatric Society

President: Dr. Joseph C. Jaudon, 337 N. Euclid Ave., St. Louis.
Secretary-Treasurer: Dr. Gilbert B. Forbes, 500 S. Kingshighway, St. Louis 10.
Time: Second Thursday of each month from October to May, inclusive.

Seattle Pediatric Society

President: Dr. Norman W. Murphy, 1300 Madison St., Seattle 4.
Secretary: Dr. David M. Harris, 630 Medical Arts Bldg., Seattle 1.
Place: College Club. Time: Third Friday of each month from September to June at 6:30 p. m.

Southwestern Pediatric Society

President: Dr. Robert J. Dostal, 710 Wilshire Blvd., Santa Monica, Calif.
Secretary: Dr. H. M. Van Dyke, 541 E. Broadway, Long Beach, Calif.
Place: University Club of Los Angeles. Time: 6:30 p. m., first Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Park Bradshaw, Muskegon, Mich.
Secretary: Dr. Harry A. Towsley, 1313 E. Ann St., Ann Arbor, Mich.

Westchester County Medical Society, Pediatrics Section (New York)

President: Dr. John B. Ahouse, 27 Ludlow St., Yonkers, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.
Place: Hospitals of Westchester County. Time: Third Thursday in November, January, March and May.